M E M O R A N D U M

To:	Timothy Leighton, EPA
From:	Jonathan Cohen, ICF
Date:	15 March, 2011
Re:	Contract No.: EP-W-06-091 WA 4-02: AEATF Wipe Study Using Trigger Spray and Wipe Statistical Review for HSRB

Introduction and Summary

In January 2011, AEATF submitted the final report for their study "A Study for Measurement of Potential Dermal and Inhalation Exposure during Application of a Liquid Antimicrobial Pesticide Product Using Trigger Spray and Wipe or Ready-to-Use Wipes for Cleaning Indoor Surfaces." ICF were asked to analyze the data for Trigger Spray and Wipe from this study to investigate the relationship between dermal and inhalation exposures and the pesticide product usage. Note that much of the SAS code used for these analyses and some of the following description was adapted from Sarkar's SAS code (which, in turn, was based on code provided by the AHETF) and his June 2010 Statistical Review "Review of Statistical Analyses in Agricultural Handler Exposure Task Force (AHETF) Monographs."

The report describes the experimental study methodology and the measurements in detail. Briefly, three test sites in Fresno, CA, were selected to represent: cluster 1, an office space; cluster 2, a retail/shopping center, and; cluster 3, a meeting space. For each test site, six volunteer subjects were selected and randomly assigned different wiping time durations from 30 minutes to 210 minutes. Each subject was given inner and outer dosimeters to wear and was also given a personal air-sampling pump to monitor their inhalation exposure. Each subject then used a trigger spray bottle and rags to wipe horizontal and vertical surfaces for their assigned wiping time duration. In cluster 1, the DDAC pesticide was diluted as one part concentrated test substance and 64 parts tap water according to the product directions. In clusters 2 and 3, the directions were misinterpreted and the DDAC pesticide was diluted as one part concentrated test substance and 63 parts tap water. Subjects were allowed to take breaks on a chair away from the wiping site, as needed. The breaks were not included in the wiping time duration but the air-sampling pump remained on throughout the breaks. Although the study design was not a probability survey, some elements of the design used randomization. These statistical analyses treat the data as either a simple random sample or a stratified random sample, where the clusters are the strata.

The exposure measurements in the report were corrected for the average percentage recovery of field fortification samples and for the removal efficiency of hand wash samples. These analyses used the corrected measurements. The data in the report were entered and compiled into an Excel spreadsheet. This included the units conversion of the amounts of active ingredient from mg into pounds and of the mass from µg to mg. The report data for inhalation exposure were unchanged other than the units conversions. The dermal exposure data were used to develop exposure measurements for three dermal exposure routes, as follows:

- **Long Dermal**. This case represents the dermal exposure for a subject wearing long pants and long-sleeved shirts, without gloves. The exposure is the sum of the mass from hand wash, face and neck, and the six inner dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

- **Short Dermal**. This case represents the dermal exposure for a subject wearing short pants and short-sleeved shirts, without gloves. The exposure is the sum of the mass from hand wash, face and neck, the outer dosimeters for the lower arm and lower leg, and the six inner dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

- **Long Short Dermal**. This case represents the dermal exposure for a subject wearing long pants and short-sleeved shirts, without gloves. The exposure is the sum of the mass from hand wash, face and neck, the outer dosimeter for the lower arm, and the six inner dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

The report only considered the dermal exposure for the "Long Dermal" case, and used the same definition. However for our analyses we chose a more consistent, and more conservative (i.e., more health protective) approach to deal with values reported as being below the level of quantitation (LOQ):

Several of the measured values were below the level of quantitation (LOQ). The experimental protocol also required that measurements of the inner dosimeters were not taken if the outer dosimeter was below the LOQ. As a slightly more conservative (i.e., more health protective) approach than the method used in the report, we replaced any value that was either a non-detect or was not measured by one half the LOQ. If any inner or outer dosimeter value was below the LOQ, 3 μg, each such value was replaced by 1.5 μg = 0.0015 mg. For example, if all the inner dosimeters were below the LOQ, then the total would be replaced by 0.009 mg. If the face and neck measurement was below the LOQ, 50 ng, it was replaced by 25 ng = 0.000025 mg. All the hand wash measurements in the study were above the LOQ.

In the body of this memorandum we present the analysis of the unit or normalized exposure defined as the dermal or inhalation exposure divided by the pounds of active ingredient handled. Estimates of the arithmetic and geometric means and standard deviation as well as the 95^{th} percentile are computed using the empirical data as well as two statistical models: the lognormal simple random sampling model and the lognormal mixed model. The mixed model includes the possibility of clustering due to the effects of the location. For example, the results for different subjects at the office site might be correlated because of the physical similarities of the room, the physical similarities of the surfaces that were wiped, the building characteristics, the investigators at that location, or other factors that are due to the selected location. For each summary statistic we present confidence intervals. We also compute the fold relative accuracy of the summary statistics and compare with the study design benchmark of 3-fold accuracy. To evaluate the statistical models we present quantile-quantile plots to compare the fit of normal and lognormal distributions to the data.

The statistical models for the normalized exposure assume that the mean value of the logarithm of the exposure is equal to an intercept plus the slope times the logarithm of the amount of active ingredient used, where the slope equals 1. To test this assumption, the regression model was fitted to the data either using simple random sampling or the mixed model and a 95% confidence interval for the slope was calculated. A statistical test was used to determine if the slope was 1 or 0, corresponding either to a valid normalized exposure model or to a case where the exposure is independent of the amount of active ingredient used. We applied this test to the three dermal exposures and to the inhalation exposure using the statistical mixed model. For dermal exposures it is reasonable to assume on physical grounds that the same patterns ought to apply to any type of dermal exposure, so that the slope should either be one for all types of dermal exposure or not one for all types of dermal exposure. To evaluate this issue we applied the same proportionality test to a hypothetical all dermal exposure case representing a janitor with no clothing, using a dermal exposure estimated as the sum of the exposures measured on the face and neck, hands, and all the inner and outer dosimeters. We also developed a statistical repeated measures model to analyze all three types of dermal exposure in a single statistical

model, accounting for within-worker correlations and within-location clustering. We also evaluated quadratic regression models.

The results for long dermal and long short dermal exposure routes show that the estimated intra-cluster correlation (ICC) coefficient is zero, which implies that there are no clustering and location effects. However, the estimated intra-cluster correlation (ICC) coefficient for short dermal is 0.2 and for inhalation exposure is 0.3, which implies that there are some clustering and location differences, which one can hypothesize as being primarily due to differences in the wiping surfaces between different buildings.

The mixed model results for the four dermal exposure routes all show a positive estimated slope but give inconsistent results for the tests of proportionality (slope equals one) and independence (slope equals zero). At the 5% level, the proportionality is rejected for long dermal and short dermal, but proportionality is not rejected for long short dermal and all dermal. At the 5% level, the independence is rejected for short dermal, long short and all dermal, but independence is not rejected for long dermal. Using the repeated measures model, proportionality and independence are both rejected. The mixed model results for inhalation exposure show a small slope of 0.2 and the proportionality is rejected.

The appendix gives the detailed results of the corresponding analyses when the exposure is normalized by the wiping duration. The appendix also includes an analysis of inhalation exposure normalized by the product of the pounds of active ingredient handled and the wiping duration, and an analysis of inhalation exposure normalized by the surface area wiped. The results show similar patterns to the normalization by amount of active ingredient handled but the slopes are lower, showing less support for those alternative exposure models. For inhalation, the data suggest that the exposure is either independent of any of these normalizing variables or is a non-linear function of these normalizing variables. A summary comparing the normalizing approaches is presented at the end of this memorandum. The mixed model analyses show that in most cases (including the repeated measures model), the best of the normalizing options considered is the amount of active ingredient handled for dermal exposures, and is the surface area wiped for inhalation exposure.

The inhalation exposure measure used for the main analyses presented here is the average air concentration (mg/m^3) over the entire period that the concentration was measured, which includes the breaks as well as the wiping durations. As an alternative approach we considered using the air DDAC mass (mg) which can be estimated as the average air concentration multiplied by the wiping duration (hours) and by an estimated 1 m^3/hour of air breathed in by someone doing light activity. A similar statistical analysis found that the air DDAC mass is not proportional to amount of active ingredient × wiping duration, but there is not enough evidence at the 5% level to reject proportionality for the other three normalizing variables (amount of active ingredient, wiping duration, surface area wiped). As shown in the summary table 10 below, the best-fitting model for the normalized air DDAC mass normalizes for the amount of active ingredient used. The appendix includes the detailed results for this model.

Analyses of exposure per pounds of active ingredient handled

Table 1 summarizes the normalized exposure data (per lb active ingredient handled) with the summary statistics from the 18 measurements for each exposure route.

Table 1. Summary statistics for normalized exposure.

Statistic	Normalized Long[a] Dermal (mg/lb AI)	Normalized Short[b] Dermal (mg/lb AI)	Normalized Long Short[c] Dermal (mg/lb AI)	Normalized Inhalation (mg/m^3/lb AI)
Arithmetic Mean	1065.8	1736.2	1544.7	10.2
Arithmetic Standard Deviation	853.9	1083.4	1027.2	10.8
Geometric Mean	859.2	1507.3	1325.1	6.7
Geometric Standard Deviation	1.9	1.7	1.7	2.7
Min	384.2	684.8	668.8	0.4
5%	384.2	684.8	668.8	0.4
10%	455.3	785.3	672.2	3.0
25%	551.6	1046.0	844.8	4.2
50%	731.1	1276.1	1195.0	7.4
75%	1139.9	2250.4	1927.0	12.8
90%	2780.0	2988.6	2929.7	26.5
95%	3478.6	5154.6	4841.8	46.3
Max	3478.6	5154.6	4841.8	46.3

[a]Long = Long pants and long sleeves
[b]Short = Short pants and short sleeves
[c]Long Short = Long pants and short sleeves

The summary analyses presented in Table 1 use the 18 measurements with a simple random sampling model that ignores the fact that the data were selected by choosing three "clusters" representing three different location types, and then measuring dermal and inhalation exposures on six subjects in each of the three clusters (a total of 18 different volunteer subjects). The six subjects in each cluster were randomly assigned six different amounts of wiping, as defined by the time to be spent wiping:

- 30 to < 60 minutes
- 60 to < 90 minutes
- 90 to < 120 minutes
- 120 to < 150 minutes
- 150 to < 180 minutes
- 180 to 210 minutes

The statistical analyses use the following three alternative statistical models. Let X be the normalized exposure and X = exp(Y) so that Y = log (X), where log denotes the natural logarithm. LnGM is the log of the geometric mean. Let Z95 be the 95th percentile of a standard normal distribution, approximately 1.645.

- Empirical simple random sampling model. Code "s." Assumes that the 18 values of X were randomly drawn from an unspecified distribution. Ignores clustering. Gives empirical estimates such as in Table 1 above.
    - Y = LnGM + Error. Error is independent and identically distributed with mean 0.
    - AMs = Arithmetic mean of X values
    - GMs = Geometric mean of X values = exp(LnGM) (= GMu)
    - GSDs = Geometric standard deviation of X values (= GSDu)
    - P95s = 95th percentile of X values
- Lognormal simple random sampling model. Code "u." Assumes that the 18 values of X were randomly drawn from a log-normal distribution. Ignores clustering.
    - Y = LnGM + Error. Error is normally distributed with mean 0, variance Vu, and standard deviation Su = √Vu.
    - AMu = Modeled arithmetic mean of X values = exp(LnGM) exp(½ Vu)
    - GMu = Modeled geometric mean of X values = exp(LnGM)
    - GSDu = Modeled geometric standard deviation of X values = exp(Su)
    - P95u = Modeled 95th percentile of X values = exp(LnGM) exp(Z95×Su)
- Lognormal mixed model. Code "m." Assumes that three cluster effects were randomly drawn from a normal distribution and that the 18 within-cluster error terms were independently randomly drawn from another normal distribution. The error term for each subject is the sum of the cluster effect for the subject's cluster and the within-cluster error term.
    - Y = LnGM + Cluster + Error. Cluster is normally distributed with mean 0, variance Vc, and standard deviation Sc = √Vc. Error is normally distributed with mean 0, variance Vw, and standard deviation Sw = √Vw. Define V = Vc + Vw and S = √V. V is the variance of Y, and S is the standard deviation of Y.
    - ICC = Intra-cluster correlation coefficient = Vc/V.
    - AMm = Modeled arithmetic mean of X values = exp(LnGM) exp(½ V)
    - GMm = Modeled geometric mean of X values = exp(LnGM)
    - GSDm = Modeled geometric standard deviation of X values = exp(S)
    - P95m = Modeled 95th percentile of X values = exp(LnGM) exp(Z95×S)

For the lognormal mixed model, the ICC value estimates the clustering effect and lies between 0 (no clustering) and 1 (complete clustering and negligible within-cluster variation). If ICC = 0, then the lognormal mixed model is identical to the lognormal simple random sampling model and the parameters (AM, GM, GSD, and P95) are identical for those two models.

Table 2 presents the arithmetic mean and 95th percentile estimates from the lognormal mixed model, together with 95% confidence intervals, for all the exposure routes. These are the values of AMm and P95m. The other summary statistics are presented in more detail below.

Table 2. Arithmetic mean and 95th percentile estimates from lognormal mixed model for normalized exposure.

Exposure Route	**Clothing**	**Arithmetic Mean (95% confidence interval)**	**95th percentile (95% confidence interval)**
Dermal (mg/lb AI)	Long pants and long sleeves	1047.6 (748.6, 1494.1)	2420.4 (1500.5, 3892.5)
	Short pants and short sleeves	1739.9 (1224.5, 2499.9)	3638.0 (2266.6, 5835.9)
	Long pants and short sleeves	1533.3 (1162.6, 2050.8)	3222.2 (2148.2, 4835.4)
Inhalation (mg/m^3/lb AI)		11.6 (4.8, 29.9)	37.5 (13.0, 109.6)

For each exposure route, the above three statistical models were fitted to the observed data and the summary statistics listed above were calculated together with 95% confidence intervals. The 95% confidence intervals in Table 2 were computed using a parametric bootstrap. Confidence intervals computed using a non-parametric bootstrap are presented below. For these calculations, the parametric bootstrap simulations were all generated from the fitted lognormal mixed model, even for the empirical and simple random sample summary statistics, on the basis that the mixed model is the best choice for modeling the data, even if the summary statistics are developed from a simpler statistical model.

The algorithm used was as follows:

Step 1:

Simulate 18 random variables Y, X from the estimated lognormal distribution superimposed upon the observed sampling structure ---;

C = LnGM + RanNor(Seed)×Sc;

Y = C + RanNor(Seed) ×Sw;

X = exp(Y);

where:

LnGM = intercept of mixed effect log-log regression model

Sc = square root of between cluster variance

Sw = square root of within cluster variance under mixed-effect model.

Step 2:

For Y:

Calculate GMs = exp(EAM)

Calculate GSDs = exp(Su)

Calculate AMu = GMs×exp(0.5×Su×Su)

Calculate P95u = GMs× exp(Z95×S)

Fit mixed lognormal model to simulated Y values

Under mixed-effects model:

Calculate GMm = exp(intercept of mixed-effects model)

Calculate GSDm = exp(square root (total variance V under mixed-effects model))

Calculate ICC = Vc /V

Calculate AMm = exp(intercept + 0.5×V)

Calculate P95m = exp(intercept + Z95×S)

where:

EAM = sample arithmetic average of Y

Su = standard deviation of Y

V = total variance under mixed-effects model

S = square root of V

Vc = between cluster variance.

For X:

Calculate arithmetic mean AMs

Calculate 95th percentile P95s

Step 3: Repeat Steps 1 and 2 10,000 times.

Steps 1 to 3 result in 10,000 values each for GSDs, GSDm, ICC, GMs, GMm, AMs, AMm, AMu, P95s, P95m, and P95u. 95% confidence intervals can be defined for each parameter by the 2.5th and 97.5th percentiles (lower and upper, respectively) of the bootstrap distribution of that corresponding parameter. Note that by definition, GSDs = GSDu and GMs = GMu. Also note that GMs = GMm for this situation because the experiment is balanced with 3 clusters and 6 subjects in each cluster; this implies that the intercept is the same value for both the simple random sampling and mixed models.

Fold relative accuracy (*fRA*) is a measure that can be used to determine how well a statistic can describe its population parameter. Let us assume θ is a parameter and T is the sample statistic of θ (i.e., an estimate of θ). If the 2.5th and 97.5th percentiles of the sampling distribution of T can be denoted by $T_{2.5}$ and $T_{97.5}$, respectively, then the 95th percentile of sample fold relative accuracy can be theoretically calculated using the following formula provided in the AHETF Governing Document (AHETF, 2007; pg. 136):

$$fRA_{95} = \text{Max}\ (T_{97.5} / \theta, \theta / T_{2.5})$$

The actual value of θ is unknown. Thus, fRA_{95} was calculated by substituting θ with T. If the fRA_{95} of a statistic were equal to 3, then it would be correct to say: "At least 95% of the time the sample statistic will be accurate to within 3-fold of the population value". According to the AHETF Governing Document, the statistical design of the exposure monitoring study should be adequate to produce a fRA_{95} less than or equal to 3. Thus the confidence intervals calculated in the above algorithm can be used to estimate the fold relative accuracy and compare the observed fRA with the study design benchmark of 3. If the observed fold relative accuracy is greater than 3, this means that the experiment did not meet the benchmark, which would be due to differences between the distributions of the CMA data used to design the study and the experimental data collected in the study. If the fold relative accuracy benchmark is not met, then it might

be desirable to collect more data for this scenario in order to meet the benchmark. Fold relative accuracy was not computed for the ICC since the estimated ICC is 0 in many cases.

The HSRB reviewers of the statistical analyses of the Mop Study ("AEATF Mop Study Statistical Review for HSRB," 19 November 2010, original version dated 28 September, 2010) suggested that a non-parametric bootstrap approach should also be considered. The non-parametric bootstrap method should be more robust since it does not assume that the fitted parametric model is the correct one. For the non-parametric bootstrap, exactly the same approach was used except that Step 1 above is replaced by the following:

Step 1:

Simulate 18 random variables Y, X by resampling at random with replacement from the original data:

For Cluster j, the original exposure data are X(1), X(2), …, X(n_j), where n_j is the number of workers in cluster j (n_j equals 6 for the wipe study data).

Sample n_i values at random with replacement from the exposure values X(1), X(2), …, X(n_j). This gives the 6 simulated random

Repeat for all three clusters. (j = 1, 2, and 3).

Y = log(X).

The Y, X values were independently resampled from the three clusters in order to preserve the covariance structure.

Tables 3 to 6 present the estimates, parametric and non-parametric confidence intervals and fold relative accuracy values for all the summary statistics for the three dermal and one inhalation exposure routes, respectively.

Table 3. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized long dermal exposure (mg/lb AI).

		Parametric Bootstrap			**Non-parametric Bootstrap**		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.9	1.5	2.3	1.2	1.5	2.1	1.3
GSDm	1.9	1.5	2.3	1.2	1.5	2.2	1.3
ICC	0.0	0.0	0.4		0.0	0.6	
GMs	859.2	626.2	1185.7	1.4	669.4	1129.4	1.3
GMm	859.2	626.2	1185.7	1.4	669.4	1129.4	1.3
AMs	1065.8	736.7	1468.3	1.4	737.4	1441.4	1.4
AMu	1045.6	745.7	1483.8	1.4	733.3	1452.5	1.4
AMm	1047.6	748.6	1494.1	1.4	740.2	1512.2	1.4
P95s	3478.6	1484.4	5660.2	2.3	1185.7	3478.6	2.9
P95u	2408.6	1483.8	3811.5	1.6	1297.7	3673.4	1.9
P95m	2420.4	1500.5	3892.5	1.6	1342.7	4030.2	1.8

Table 4. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized short dermal exposure (mg/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.7	1.4	2.0	1.2	1.4	1.9	1.2
GSDm	1.7	1.4	2.1	1.2	1.4	2.0	1.2
ICC	0.2	0.0	0.6		0.0	0.7	
GMs	1507.3	1076.5	2132.2	1.4	1233.9	1868.7	1.2
GMm	1507.3	1076.5	2132.2	1.4	1233.9	1868.7	1.2
AMs	1736.2	1209.0	2447.8	1.4	1337.2	2201.4	1.3
AMu	1727.8	1216.4	2465.3	1.4	1334.3	2216.3	1.3
AMm	1739.9	1224.5	2499.9	1.4	1342.0	2277.7	1.3
P95s	5154.6	2251.5	7514.0	2.3	2516.6	5154.6	2.0
P95u	3560.0	2245.3	5575.9	1.6	2295.0	5013.8	1.6
P95m	3638.0	2266.6	5835.9	1.6	2327.2	5497.9	1.6

Table 5. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized long short dermal exposure (mg/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.7	1.4	2.1	1.2	1.4	1.9	1.2
GSDm	1.7	1.4	2.1	1.2	1.4	2.0	1.2
ICC	0.0	0.0	0.4		0.0	0.6	
GMs	1325.1	1016.8	1735.7	1.3	1063.3	1667.7	1.3
GMm	1325.1	1016.8	1735.7	1.3	1063.3	1667.7	1.3
AMs	1544.7	1150.0	2021.2	1.3	1158.1	1994.4	1.3
AMu	1531.9	1160.2	2038.8	1.3	1154.1	1997.7	1.3
AMm	1533.3	1162.6	2050.8	1.3	1157.9	2047.7	1.3

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
P95s	4841.8	2138.5	6653.3	2.3	2071.1	4841.8	2.3
P95u	3213.0	2138.3	4753.6	1.5	2009.8	4612.2	1.6
P95m	3222.2	2148.2	4835.4	1.5	2034.8	4972.7	1.6

Table 6. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation exposure (mg/m^3/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	2.7	1.9	4.1	1.5	1.7	3.9	1.6
GSDm	2.9	1.9	4.7	1.6	1.8	4.5	1.6
ICC	0.3	0.0	0.7		0.0	0.7	
GMs	6.7	3.1	14.4	2.2	4.5	9.5	1.5
GMm	6.7	3.1	14.4	2.2	4.5	9.5	1.5
AMs	10.2	4.5	25.2	2.5	6.5	14.5	1.6
AMu	11.0	4.7	26.6	2.4	7.0	17.0	1.6
AMm	11.6	4.8	29.9	2.6	7.2	19.8	1.7
P95s	46.3	12.8	153.4	3.6	13.0	46.3	3.6
P95u	34.8	12.6	92.8	2.8	16.2	61.1	2.1
P95m	37.5	13.0	109.6	2.9	16.8	74.5	2.2

Tables 3 and 5 show that the ICC estimated value is zero for the long dermal and long short dermal exposure routes showing that the estimated mixed and simple random sampling models are the same for those cases and that there is no variation between the different locations. Tables 4 and 6 show that the ICC estimated value is non-zero for the short dermal and inhalation exposure routes showing that the estimated mixed and simple random sampling models are not the same for those cases and that there is some variation between the different locations. All of the fold relative accuracy values met the study design benchmark of 3 except for the empirical 95th percentile for the normalized inhalation exposure. The parametric bootstrap confidence intervals were similar to the non-parametric bootstrap confidence intervals for the dermal exposure routes, but were generally wider than the non-parametric bootstrap confidence intervals for the inhalation exposure.

Quantile-quantile plots of the normalized exposure values were used to evaluate whether the data were lognormally distributed, as implied by the assumed statistical models. In each case the quantile-quantile plot compared the observed quantiles of the 18 measured values with the corresponding quantiles of a normal or lognormal distribution. A perfect fit would imply that the plotted values lie in a straight line. The quantile plots are presented in Figures 1 to 8. They

clearly show that the lognormal distribution is a better fit than a normal distribution, and that the lognormal distribution fits reasonably well for all of the exposure routes.

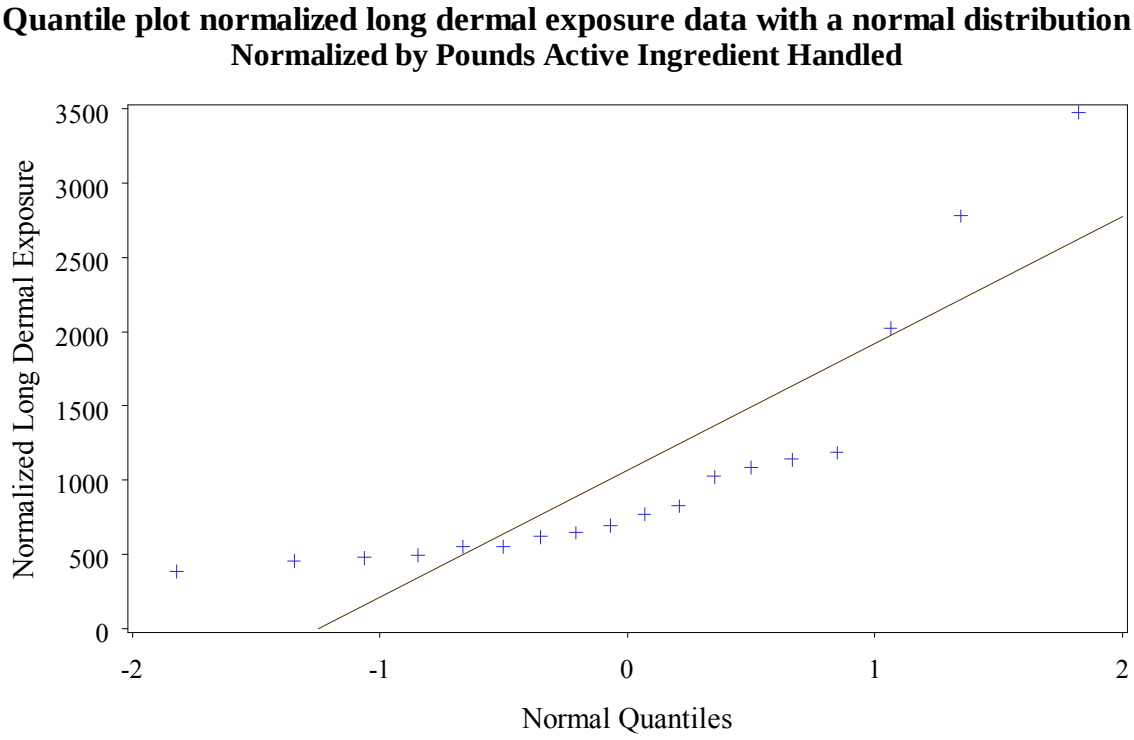

Figure 1

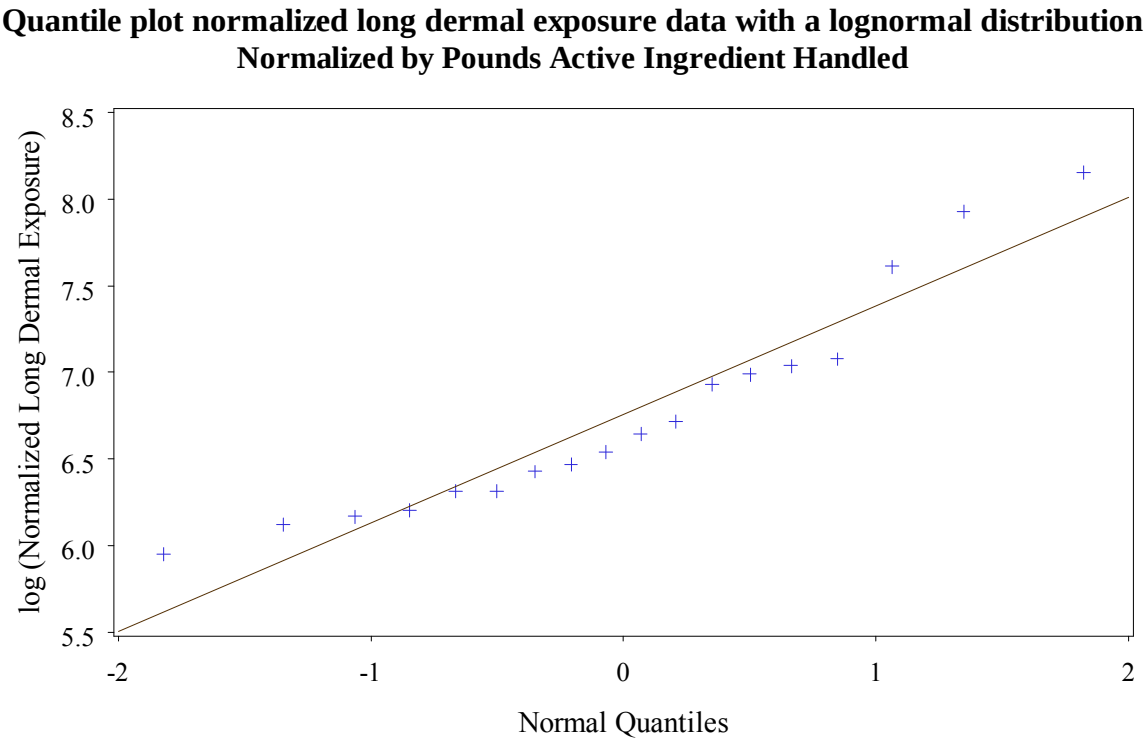
Quantile plot normalized long dermal exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized Long Dermal Exposure)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
-2
-1
0
1
2
Normal Quantiles

Figure 2

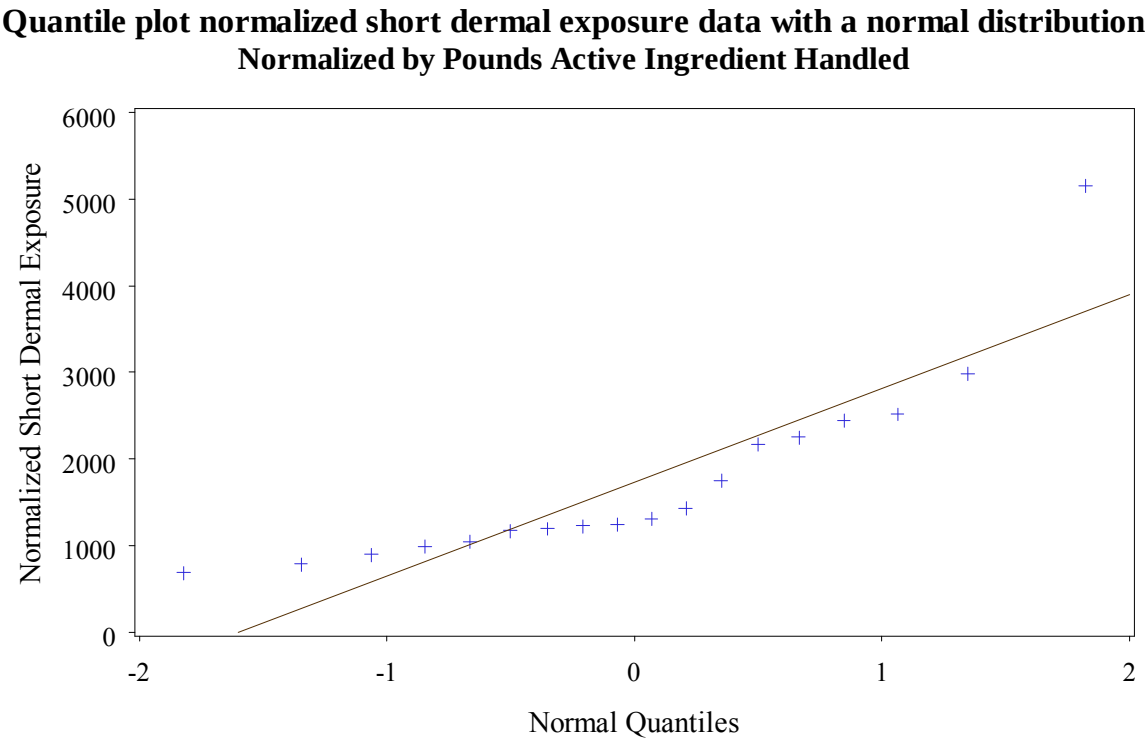
Quantile plot normalized short dermal exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized Short Dermal Exposure
6000
5000
4000
3000
2000
1000
0
-2
-1
0
1
2
Normal Quantiles

Figure 3

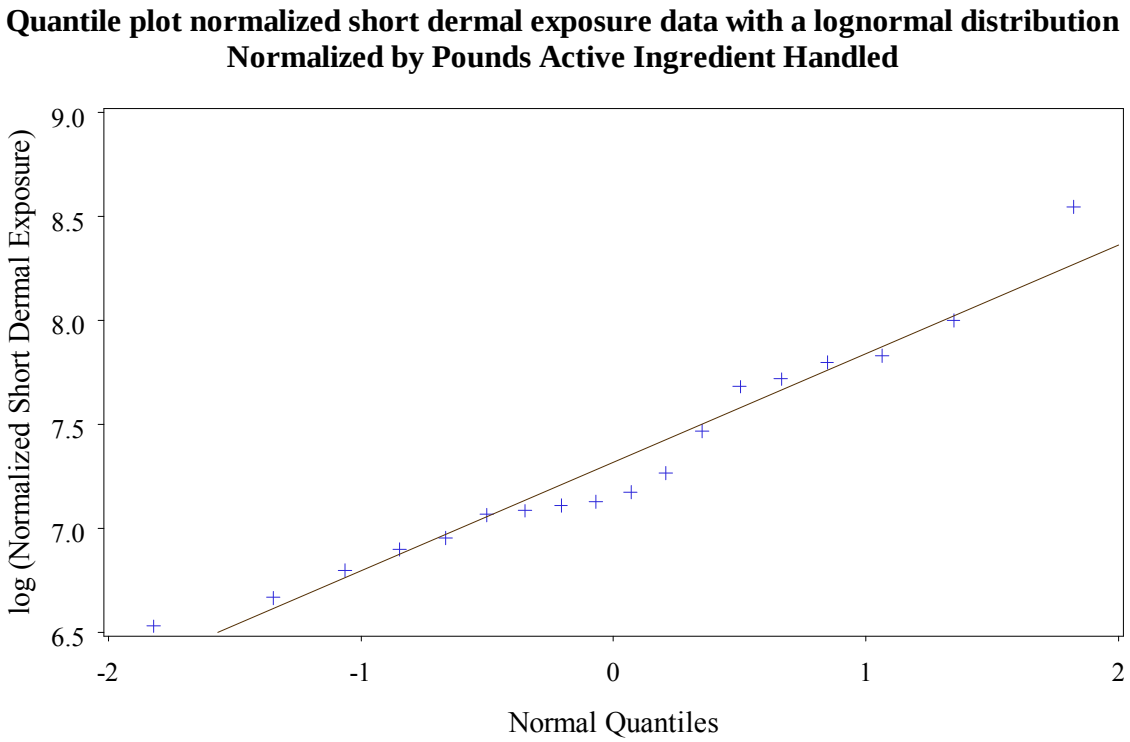
Quantile plot normalized short dermal exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized Short Dermal Exposure)
9.0
8.5
8.0
7.5
7.0
6.5
-2
-1
0
1
2
Normal Quantiles

Figure 4

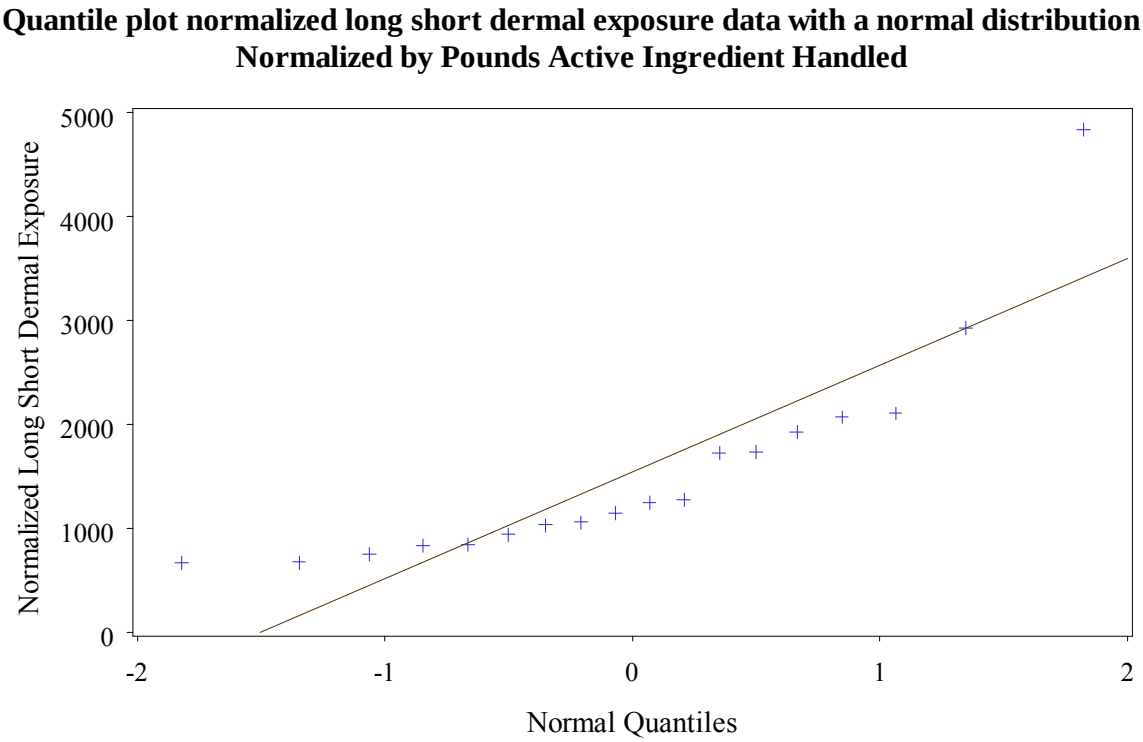
Quantile plot normalized long short dermal exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized Long Short Dermal Exposure
5000
4000
3000
2000
1000
0
-2
-1
0
1
2
Normal Quantiles

Figure 5

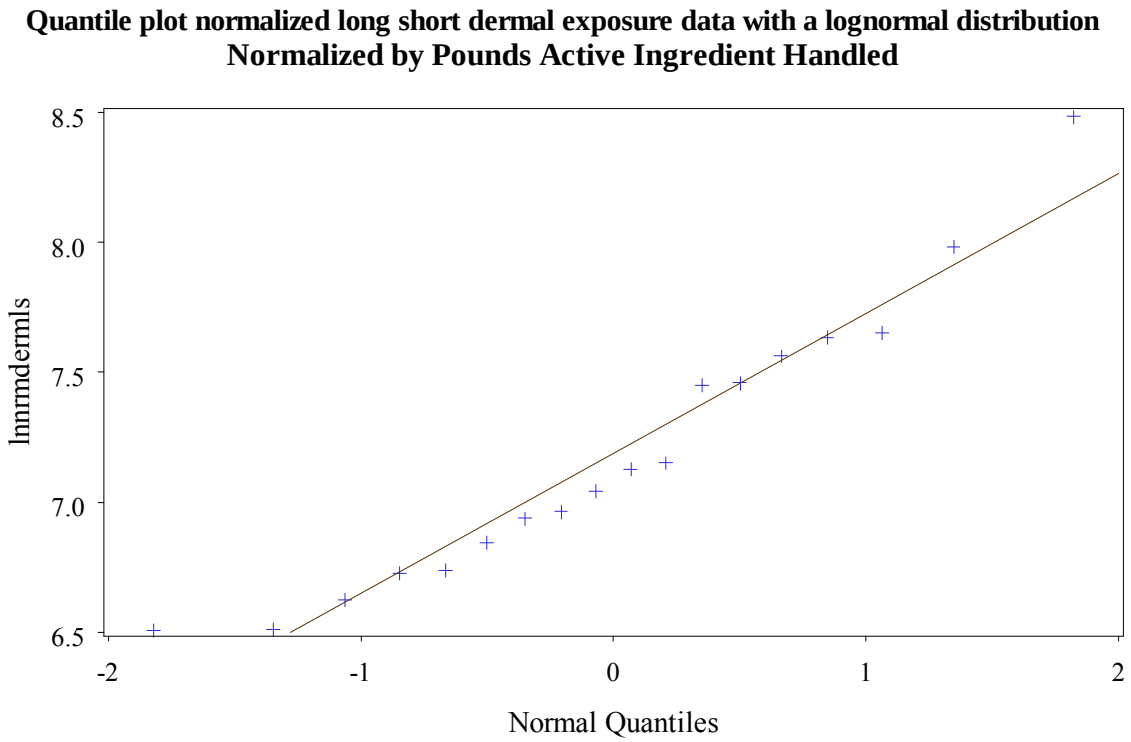
Quantile plot normalized long short dermal exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
lnnrmdermls
8.5
8.0
7.5
7.0
6.5
-2
-1
0
1
2
Normal Quantiles

Figure 6

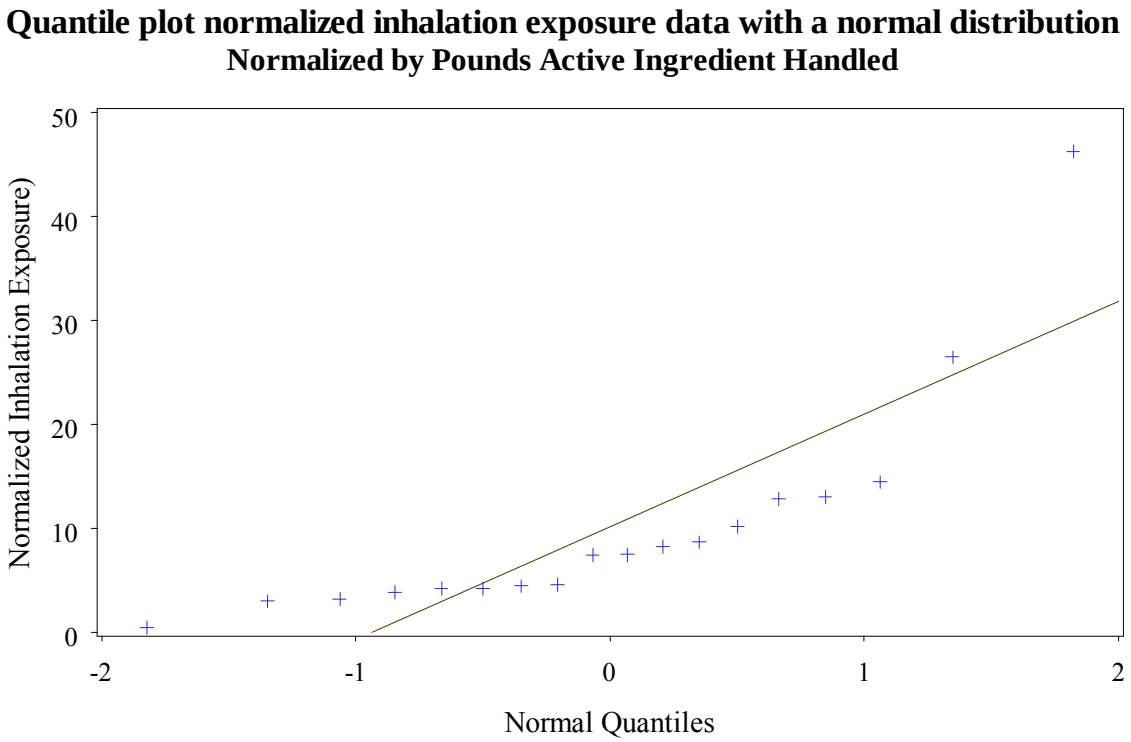
Quantile plot normalized inhalation exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled
Normalized Inhalation Exposure)
50
40
30
20
10
0
-2
-1
0
1
2
Normal Quantiles

Figure 7

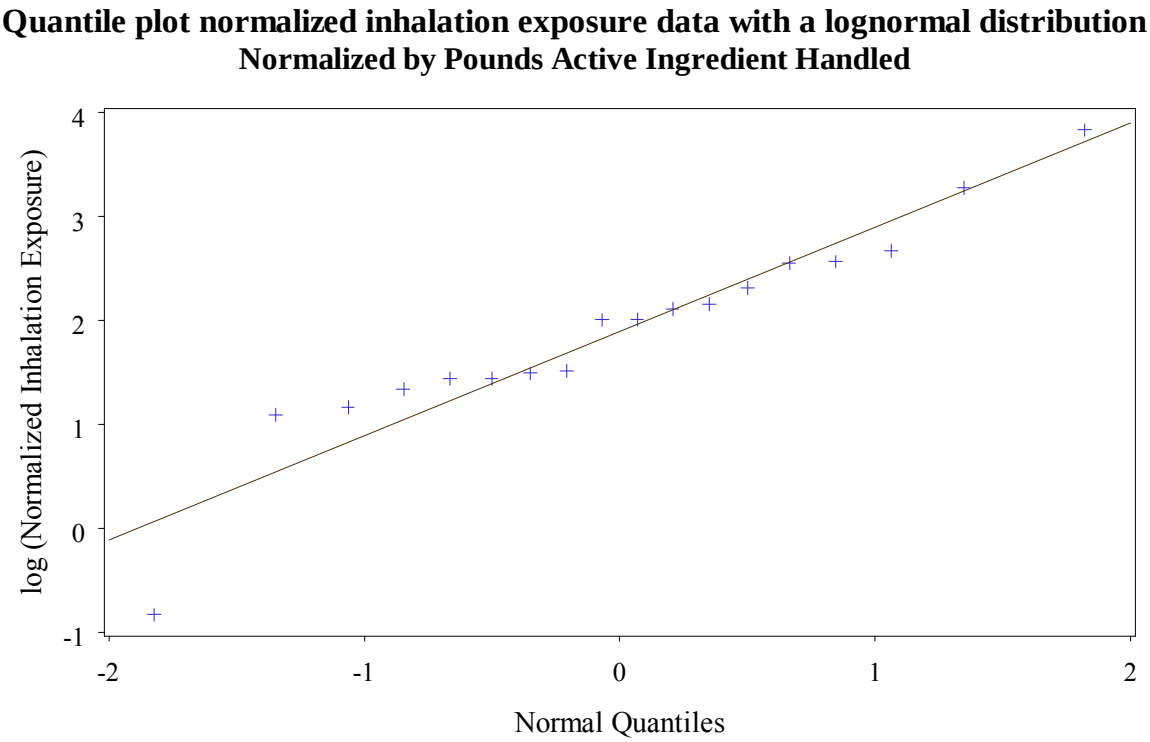
Quantile plot normalized inhalation exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled
log (Normalized Inhalation Exposure)
4
3
2
1
0
-1
-2
-1
0
1
2
Normal Quantiles

Figure 8

These statistical models for the normalized exposure assume that the exposure is proportional to the normalizing variable pounds of active ingredient handled. More precisely, the assumed statistical models are of the form

Log (Exposure) = Intercept + Slope × Log (Pounds of Active Ingredient) + Error Terms

where Slope = 1. Possible alternative models include the same formulation with a Slope of zero, implying that the exposure does not depend upon the amount of active ingredient handled, even though the wiping times, and hence the amount of active ingredient handled, varied between the subjects as part of the study design. Other possible models include the same model with a slope not equal to zero or one, the quadratic models discussed below, or models with more complicated relationships between the exposure and the experimental conditions. To evaluate whether the slope is zero, one, or other possible values, we fitted the above statistical model and computed confidence intervals for the slope. In the appendix we investigate normalizing by the wiping duration or, for inhalation exposure, by the product of the pounds of active ingredient and wiping duration and by the number of wipes used.

To analyze the proportionality, we also considered an additional hypothetical clothing scenario with no clothing at all. The dermal exposure for the No clothing scenario was calculated by summing all the inner and outer dermal exposure measurements:

All Dermal. This case represents the dermal exposure for a subject wearing no clothes. The exposure is the sum of the mass from hand wash, face and neck, and the six inner and six outer dosimeters (lower arm, upper arm, lower leg, upper leg, front torso, rear torso).

We can use these statistical models to calculate confidence intervals for the slope. The calculation of the confidence intervals depends upon the value of the denominator degrees of freedom for the mixed models used. A review of the alternative methods for calculating the denominator degrees of freedom for fixed effects in a mixed model using the SAS MIXED procedure is given in an article by Schaalje et al[1]. Based on that article, the following Table 7 summarizes the five available methods:

Table 7. SAS Methods for Computing the Fixed Effects Denominator Degrees of Freedom in PROC MIXED.

DDF Method	**SAS Abbreviation**	**Comments**
Residual	residual	Uses residual degrees of freedom. Ignores covariance structure as defined by the RANDOM and REPEATED statements. This method is not recommended.
Containment	contain	Default method when RANDOM statements are present. Accounts for the minimum contribution of the random effects that syntactically

[1] Schaalje, G. B., J. B. McBride, G. W. Fellingham. "Approximations to Distributions of Test Statistics in Complex Mixed Linear Models Using SAS® Proc MIXED" *Proceedings of the Twenty Sixth Annual SAS Users Group International Conference*. April 2001. Long Beach, CA. ISBN 1-58025-864-6. SAS Institute, Cary, NC 27513.

DDF Method	SAS Abbreviation	Comments
		contain the fixed effects of interest.
Between-Within	bw	Default method when REPEATED statements are present and RANDOM statements are not present. Only exact when the data are balanced and the design is a repeated measures design with compound symmetry, and where the levels of the within-subjects effects are not replicated within any of the subjects. Otherwise the method is at best approximate and can be unpredictable.
Satterthwaite / Fai-Cornelius	satterth	Designed to approximate the denominator degrees of freedom for split-plot designs with complicated covariance structures and/or unbalanced data sets.
Kenwood-Rogers	kr	Designed to approximate the denominator degrees of freedom for designs with complicated covariance structures and/or unbalanced data sets. Results from simulations suggest better performance than the Satterthwaite method. If a covariance parameter has zero variance then this method ignores that covariance.

To interpret this table for this study, note that the RANDOM statement was used to define the cluster effect. If the ICC equals zero, then there is no clustering and the cluster variance equals zero. The REPEATED statement was used to define the repeated measures model. A balanced data set is one where each treatment combination is applied to the same number of subjects. For this study, this implies that there are the same number of workers in every cluster, and each worker has the same number of measured exposure values.

The study data were balanced since there were 6 workers in each cluster, each with the same number of exposure measurements. Based on this summary, the recommended methods are the containment method for the mixed models when the ICC parameter is zero, and the Kenwood-Rogers method for the mixed models where the ICC parameter is non-zero or for the repeated measures model (detailed below). (For other applications, the Kenwood-Rogers method would be preferred in general if the data are sufficiently unbalanced, but it is not easy to provide rules as to how this should be defined.) The confidence intervals for the regression coefficients presented in this memorandum follow these recommendations. In particular, since the ICC parameters in the mixed regression models for the logarithm of the long

dermal, short dermal, and long short dermal exposure against the logarithm of the pounds of active ingredient handled were all zero, the containment method was used in those cases. However, since the ICC parameter in the mixed regression models for the logarithm of the all dermal and inhalation exposure against the logarithm of the pounds of active ingredient handled was non-zero, the Kenwood-Rogers method was used for those mixed models. (As noted above the ICC for the normalized short dermal exposure was estimated to be 0.2, a small but nonzero value; this is not inconsistent with the regression analysis because the regression model allows the slope to be arbitrary but the model for the normalized short dermal exposure assumes the slope is equal to 1.) Note that this issue does not impact the calculated confidence intervals for the summary statistics in Tables 2 to 6, since they used a bootstrap method.

Table 8 shows the 95% confidence intervals for the slope calculated from the above model, either assuming the lognormal simple random sampling model for the errors or the lognormal mixed model for the errors. Also shown is the width of the confidence interval for the slope. A confidence interval that includes one but not zero supports the assumptions of the normalized exposure models. A confidence interval that includes zero but not one suggests that the exposure does not depend on the amount of active ingredient handled. A confidence interval that includes both zero and one suggests that either the basic statistical model is incorrect or there are not enough data to statistically infer whether the slope is zero or one. The Repeated Measures statistical model (bottom row) is described and discussed below.

Table 8. 95 percent confidence intervals for the slope of log exposure versus log pounds active ingredient handled.

Exposure Route	Clothing	Model	Estimate	Lower	Upper	Confidence Interval Width
Dermal (mg)	Long pants and long sleeves	Mixed	0.37	-0.02	0.76	0.78
		Simple Linear	0.37	-0.01	0.76	0.77
	Short pants and short sleeves	Mixed	0.57	0.21	0.93	0.73
		Simple Linear	0.57	0.21	0.93	0.72
	Long pants and short sleeves	Mixed	0.58	0.20	0.97	0.77
		Simple Linear	0.58	0/21	0.96	0.76
	None	Mixed	0.74	0.35	1.12	0.77
		Simple Linear	0.65	0.27	1.02	0.74
Inhalation (mg/m^3)		Mixed	0.25	-0.46	0.96	1.42
		Simple Linear	0.15	-0.53	0.83	1.36
Dermal (mg)	Any	Repeated Measures	0.49	0.03	0.96	0.93

For the long dermal exposure route, the confidence interval for the slope includes 0 and excludes 1, and the estimated slope is approximately 0.4. Thus the assumption of proportionality was rejected at the 5% level but the assumption of independence was not rejected. For the short dermal exposure route, the confidence interval for the slope excludes 0 and excludes 1, and the estimated slope is approximately 0.6. Thus the assumption of proportionality was rejected at the 5% level as was the assumption of independence. For the long short and all dermal exposure routes, the confidence interval for the slope includes 1 and excludes 0, and the estimated slope is approximately 0.6. Thus the assumption of proportionality was rejected at the 5% level and the assumption of independence was not rejected. For the inhalation exposure, there is sufficient evidence to reject the hypothesis of a slope of 1 at the 5% significance level.

Based on the available CMA data, the experiment was designed to be able to detect whether the slope was 0 or 1 using a test at the 5% significance level with a power of 80%. On that basis, the experiment was designed to make the expected confidence interval width equal to 1.4:

Given:

Power = 1 – P(type II error) = 1-β = 0.80;

Significance level = P(type I error) = α = 0.05;

(Eq. 1) Predicted 95% Confidence Interval (two sided) for the regression slope = Sample estimate of slope ± 1.96× Standard Error

Effect Size = $(Z_{1-\alpha/2} + Z_{1-\beta}) \times$ Standard Error

Here, Z_P is the p^{th} percentile of a standard normal distribution:

$Z_{1-\alpha/2} = Z_{0.975} = 1.96$;

$Z_{1-\beta} = Z_{0.80} = 0.84$

$Z_{1-\alpha/2} + Z_{1-\beta} = 2.8$

(Eq. 2) Standard Error = Effect Size ÷ 2.8

Substituting Standard Error into (Eq. 1):

Predicted 95% Confidence Interval (two sided) for the regression slope = Sample estimate ± 1.96× (Effect Size ÷ 2.8) = Sample estimate ± 0.7×Effect Size

Here, Effect Size = 1 – 0 = 1 (i.e., slope = 1 under H_1 vs. slope = 0 under H_0)

So, expected width of confidence interval for slope parameter = 2×0.7 = 1.4

The results in Table 8 show that the actual confidence interval widths were less than 1.4 for the dermal exposure routes. However, the actual confidence interval widths were slightly greater than 1.4 for the inhalation exposure route because the standard errors of the slopes in the actual data were greater than the values estimated using the CMA data prior to the experiment.

For the simple linear regression analyses based on the simple random sampling model, the relationship between the exposure and the amount of active ingredient is displayed in the following regression plots in Figures 9 to 13.

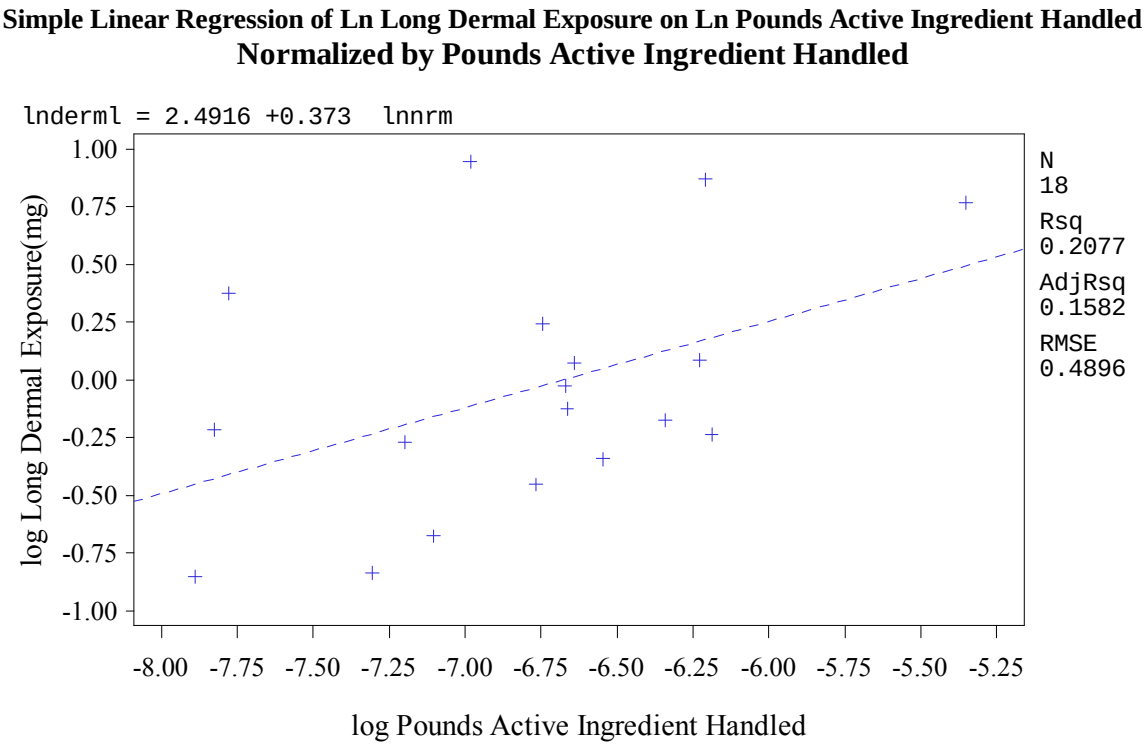
Simple Linear Regression of Ln Long Dermal Exposure on Ln Pounds Active Ingredient Handled
Normalized by Pounds Active Ingredient Handled
lnderml = 2.4916 +0.373 lnnrm
log Long Dermal Exposure(mg)
1.00
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
-8.00 -7.75 -7.50 -7.25 -7.00 -6.75 -6.50 -6.25 -6.00 -5.75 -5.50 -5.25
log Pounds Active Ingredient Handled
N
18
Rsq
0.2077
AdjRsq
0.1582
RMSE
0.4896

Figure 9

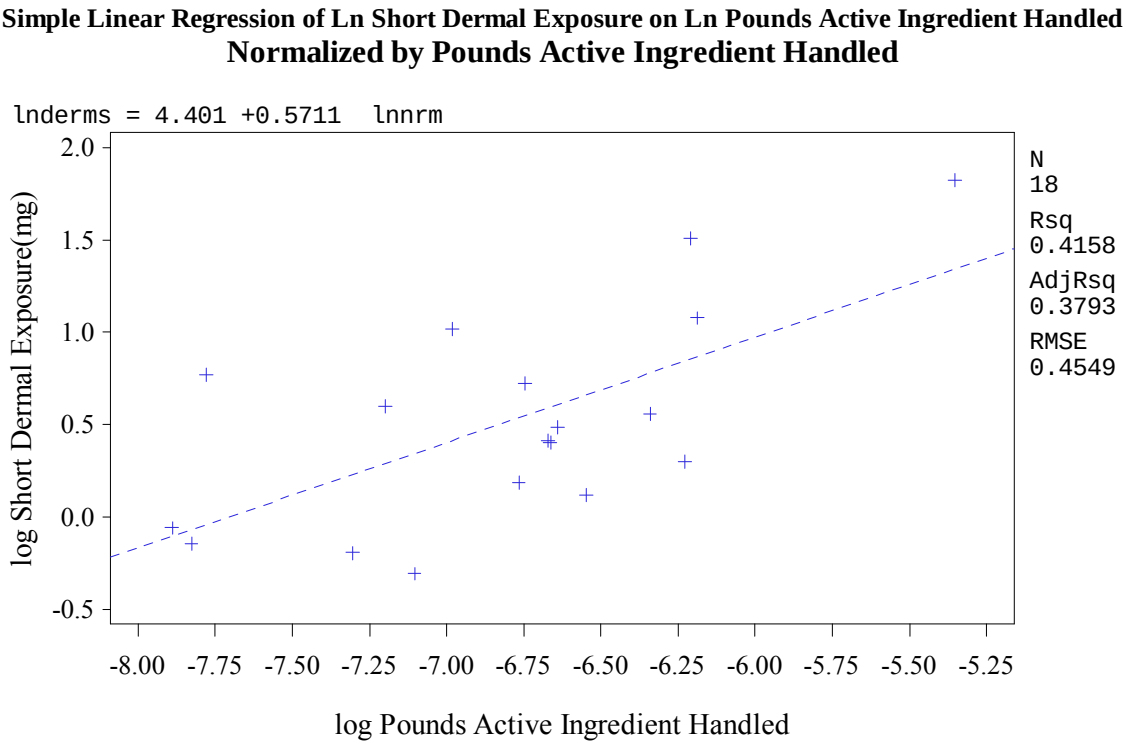
Simple Linear Regression of Ln Short Dermal Exposure on Ln Pounds Active Ingredient Handled
Normalized by Pounds Active Ingredient Handled
lnderms = 4.401 +0.5711 lnnrm
N
18
Rsq
0.4158
AdjRsq
0.3793
RMSE
0.4549
log Short Dermal Exposure(mg)
2.0
1.5
1.0
0.5
0.0
-0.5
-8.00
-7.75
-7.50
-7.25
-7.00
-6.75
-6.50
-6.25
-6.00
-5.75
-5.50
-5.25
log Pounds Active Ingredient Handled

Figure 10

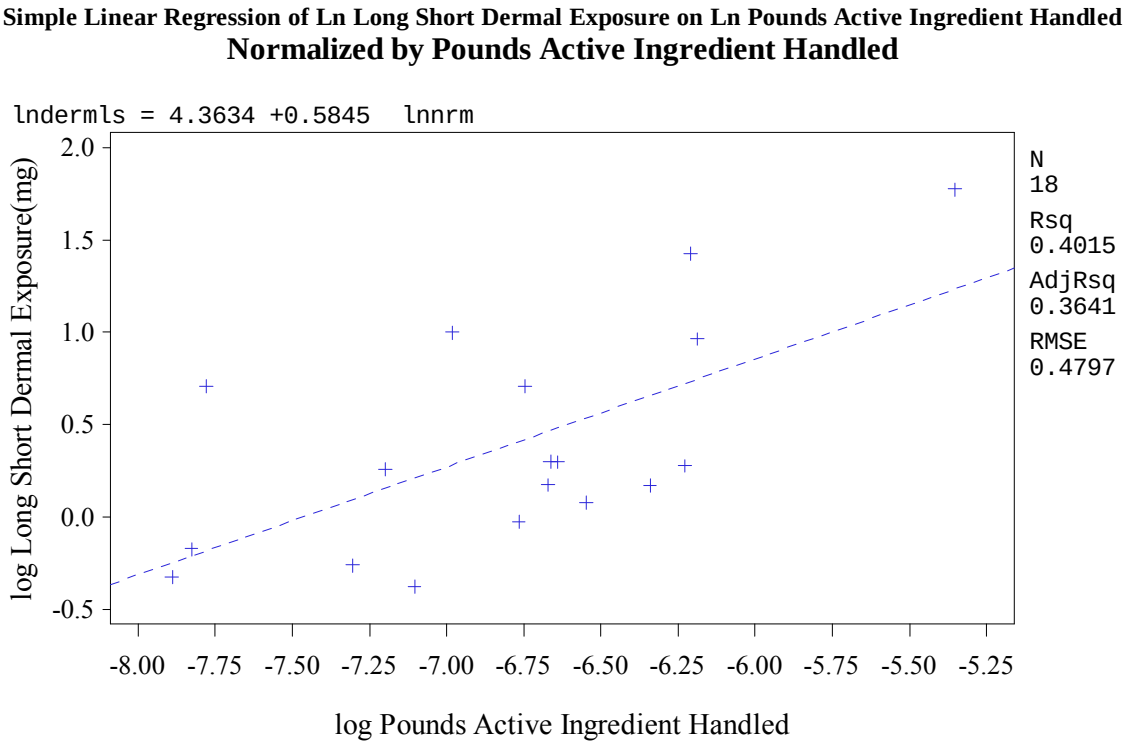
Simple Linear Regression of Ln Long Short Dermal Exposure on Ln Pounds Active Ingredient Handled
Normalized by Pounds Active Ingredient Handled
lndermls = 4.3634 +0.5845 lnnrm
N
18
Rsq
0.4015
AdjRsq
0.3641
RMSE
0.4797
log Long Short Dermal Exposure(mg)
2.0
1.5
1.0
0.5
0.0
-0.5
-8.00
-7.75
-7.50
-7.25
-7.00
-6.75
-6.50
-6.25
-6.00
-5.75
-5.50
-5.25
log Pounds Active Ingredient Handled

Figure 11

Simple Linear Regression of Ln All Dermal Exposure on Ln Pounds Active Ingredient Handled
Normalized by Pounds Active Ingredient Handled

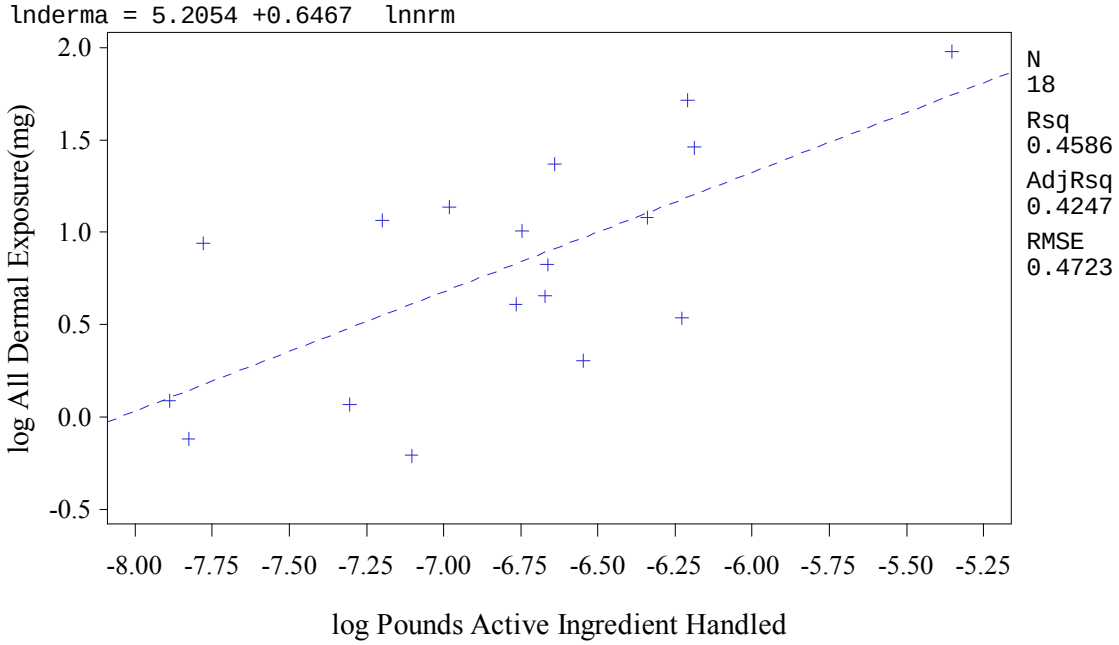

Figure 12

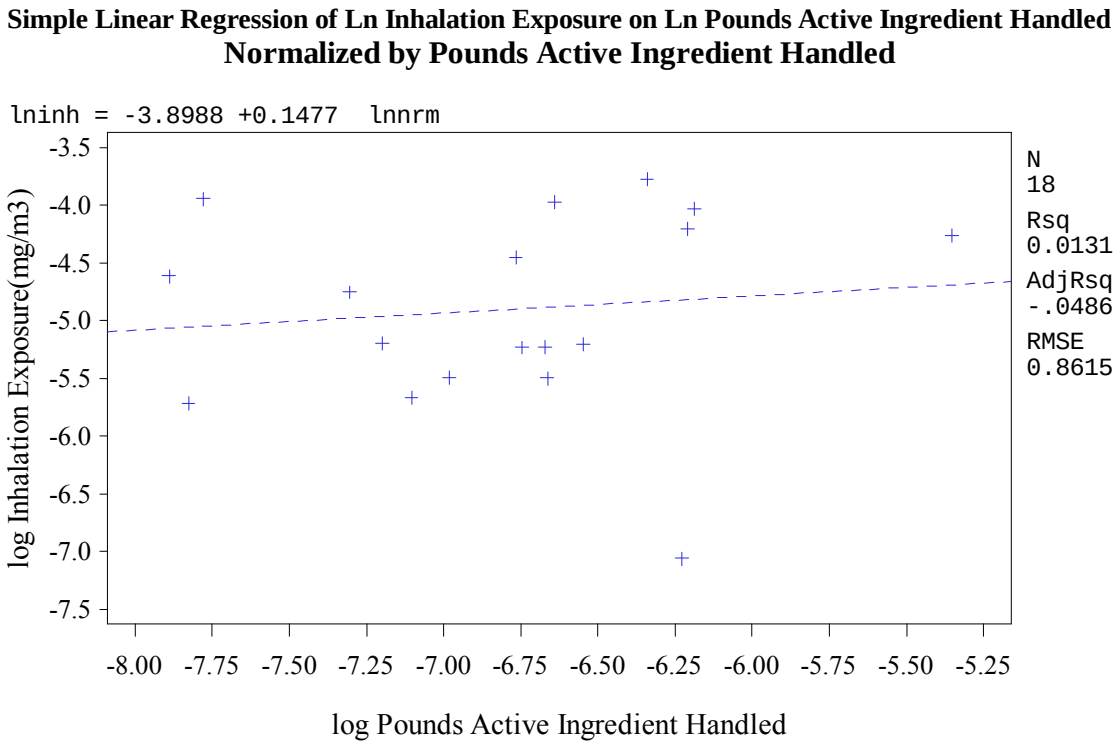
Simple Linear Regression of Ln Inhalation Exposure on Ln Pounds Active Ingredient Handled
Normalized by Pounds Active Ingredient Handled
lninh = -3.8988 +0.1477 lnnrm
log Inhalation Exposure(mg/m3)
-3.5
-4.0
-4.5
-5.0
-5.5
-6.0
-6.5
-7.0
-7.5
-8.00
-7.75
-7.50
-7.25
-7.00
-6.75
-6.50
-6.25
-6.00
-5.75
-5.50
-5.25
log Pounds Active Ingredient Handled
N
18
Rsq
0.0131
AdjRsq
-.0486
RMSE
0.8615

Figure 13

These simple linear regression results are compared with the results for the lognormal mixed models in Figures 14 to 18. Note that in the first three dermal exposure Figures 14 to 16, the regression lines are the same for the mixed and simple linear regression models because the estimated ICC parameter was zero.

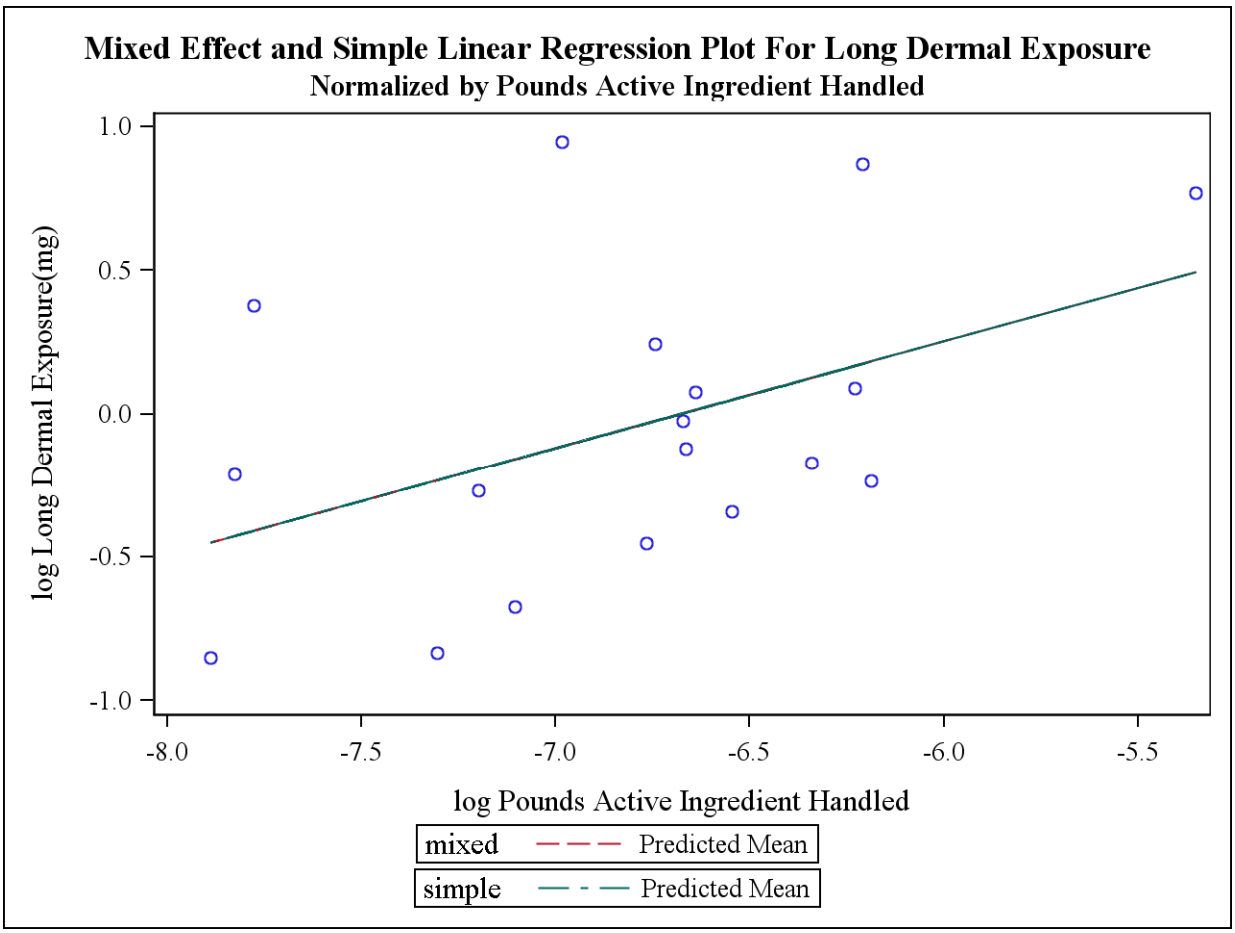

Figure 14

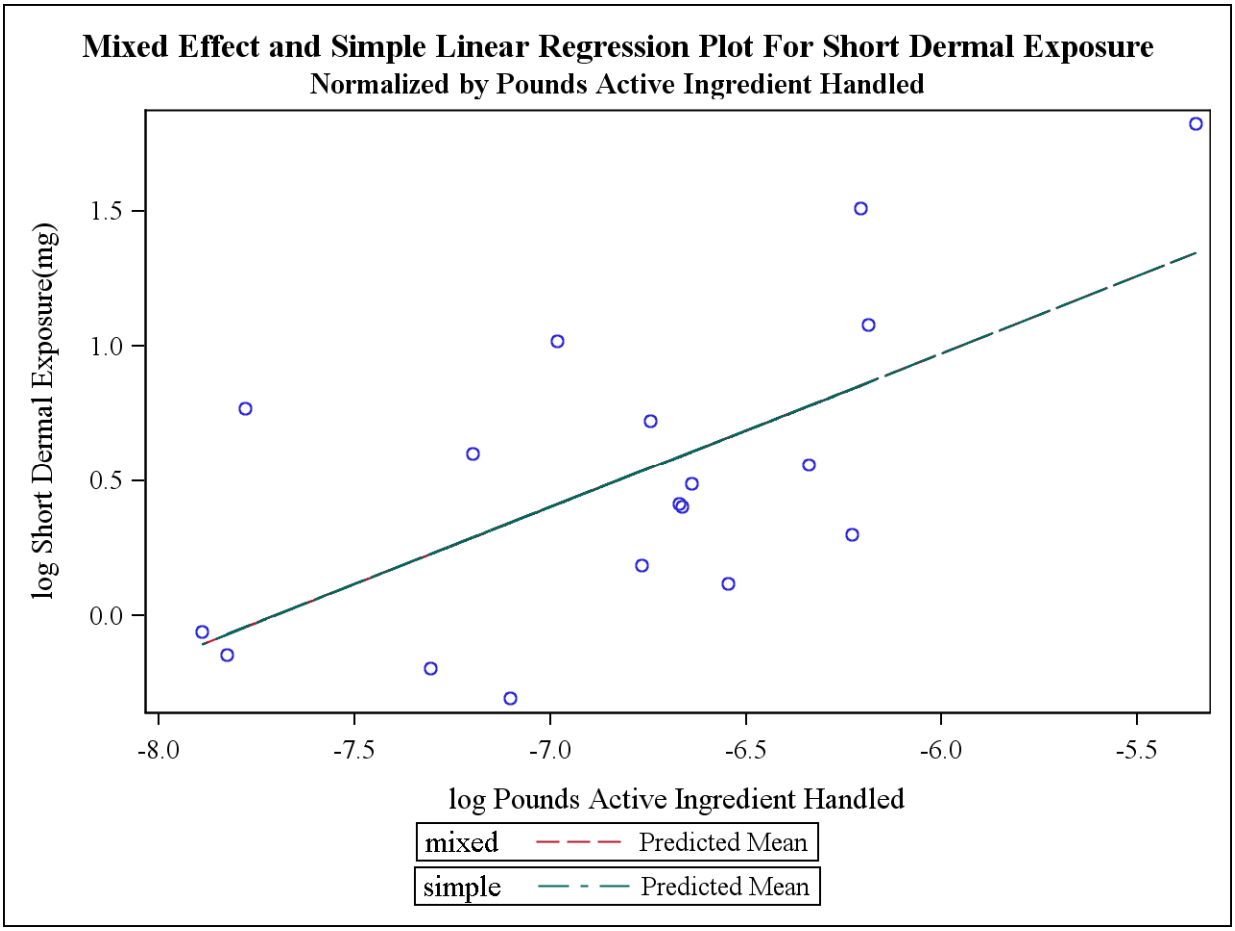
Mixed Effect and Simple Linear Regression Plot For Short Dermal Exposure
Normalized by Pounds Active Ingredient Handled
log Short Dermal Exposure(mg)
1.5
1.0
0.5
0.0
-8.0
-7.5
-7.0
-6.5
-6.0
-5.5
log Pounds Active Ingredient Handled
mixed Predicted Mean
simple Predicted Mean

Figure 15


Mixed Effect and Simple Linear Regression Plot For Long Short Dermal Exposure
Normalized by Pounds Active Ingredient Handled
log Long Short Dermal Exposure(mg)
1.5
1.0
0.5
0.0
-0.5
-8.0
-7.5
-7.0
-6.5
-6.0
-5.5
log Pounds Active Ingredient Handled
mixed Predicted Mean
simple Predicted Mean

Figure 16

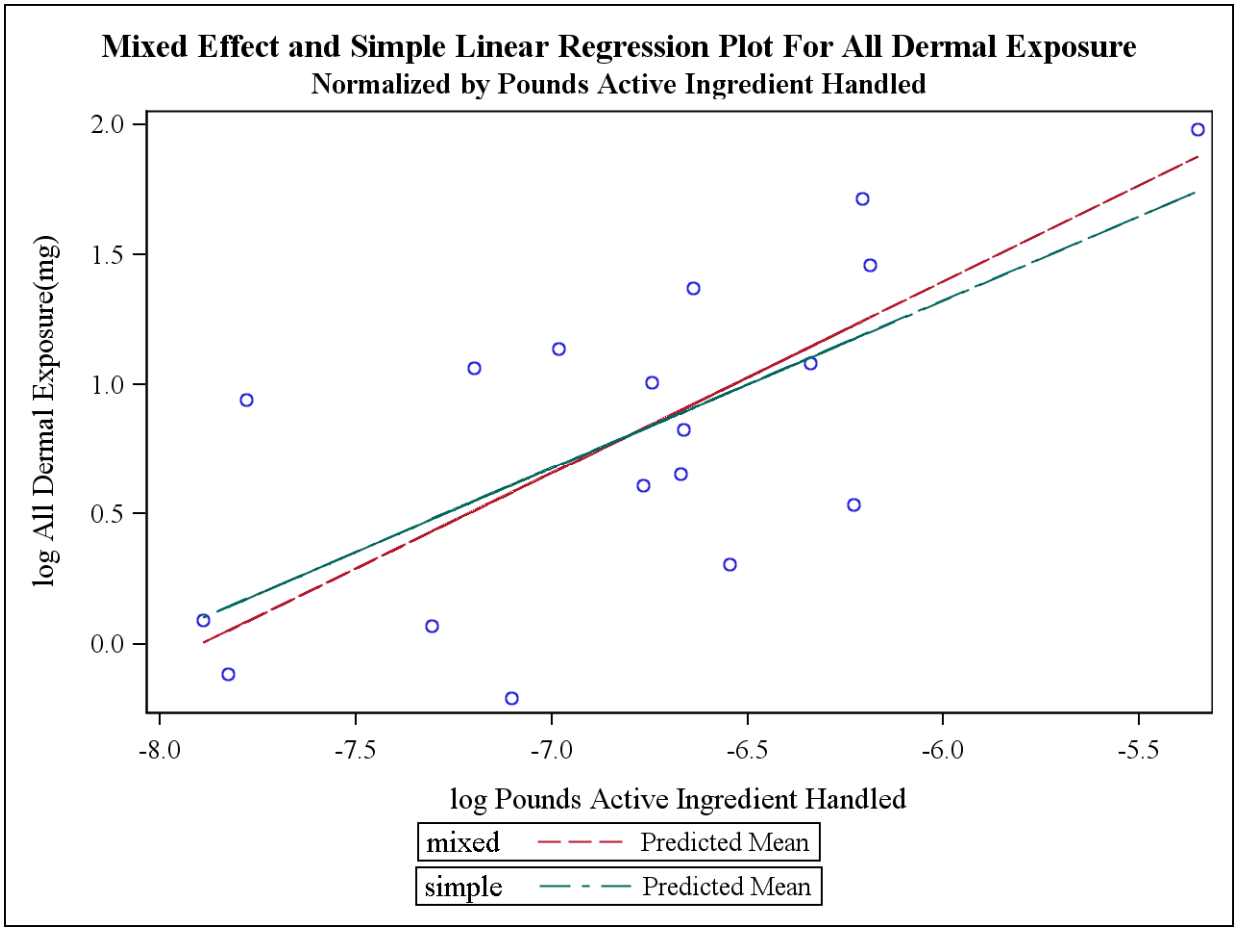
Mixed Effect and Simple Linear Regression Plot For All Dermal Exposure
Normalized by Pounds Active Ingredient Handled
log All Dermal Exposure(mg)
2.0
1.5
1.0
0.5
0.0
-8.0
-7.5
-7.0
-6.5
-6.0
-5.5
log Pounds Active Ingredient Handled
mixed
Predicted Mean
simple
Predicted Mean

Figure 17

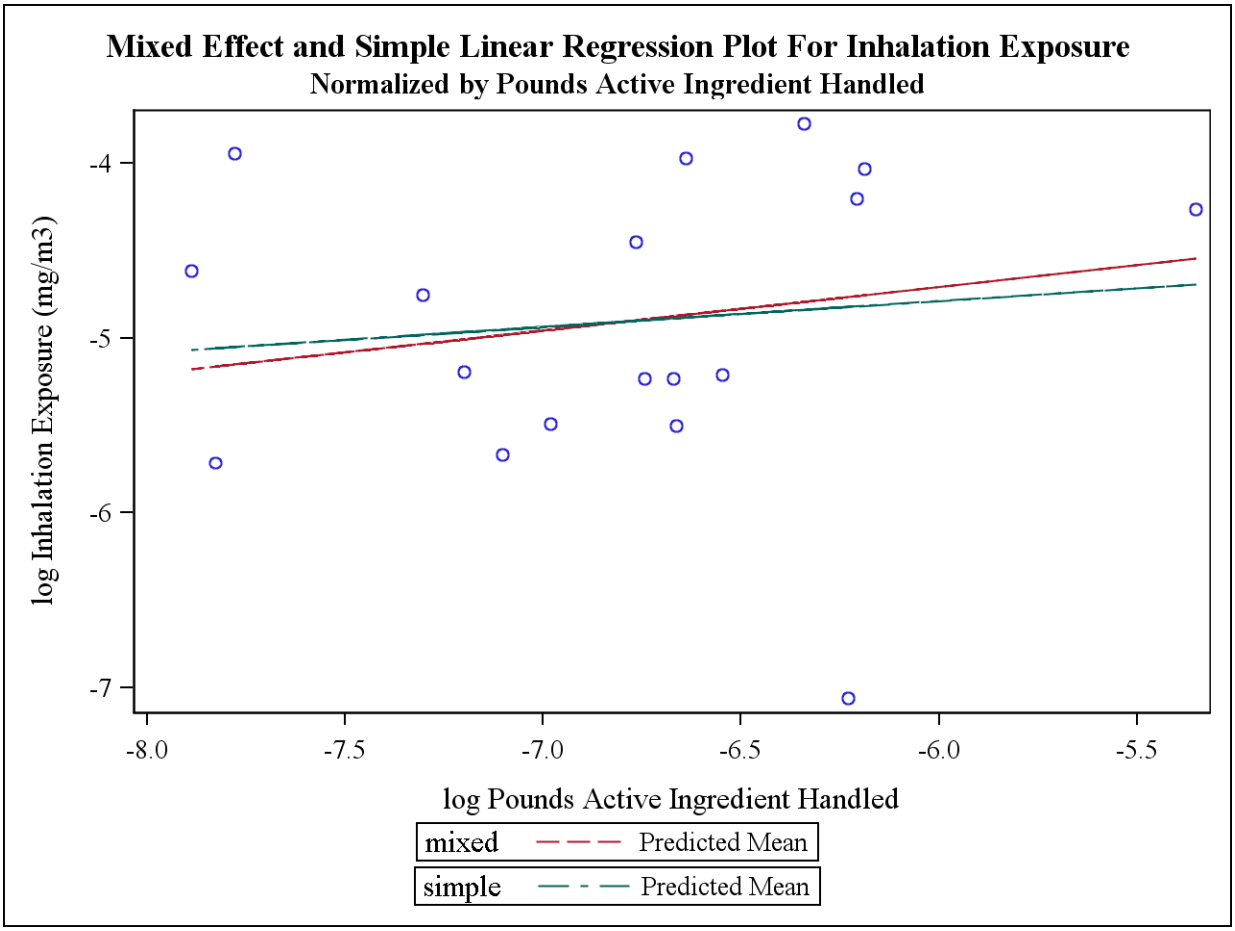
Mixed Effect and Simple Linear Regression Plot For Inhalation Exposure
Normalized by Pounds Active Ingredient Handled
log Inhalation Exposure (mg/m3)
-4
-5
-6
-7
-8.0
-7.5
-7.0
-6.5
-6.0
-5.5
log Pounds Active Ingredient Handled
mixed Predicted Mean
simple Predicted Mean

Figure 18

Finally, in Figures 19 and 20 we present regression plots showing the different regression lines for the three clusters based on the mixed models for all dermal and inhalation exposure. (For the long, short, and long short dermal exposure routes, the models predict the same values for all three clusters, i.e., they predict the values shown in Figures 14 to 16). The mixed model predicts the highest all dermal and inhalation exposures in Cluster 1 (office), and the lowest dermal all dermal and inhalation exposures in Cluster 2 (retail / shopping center), which is consistent with the data. These differences are likely attributable to the different wiping surfaces in the three buildings.

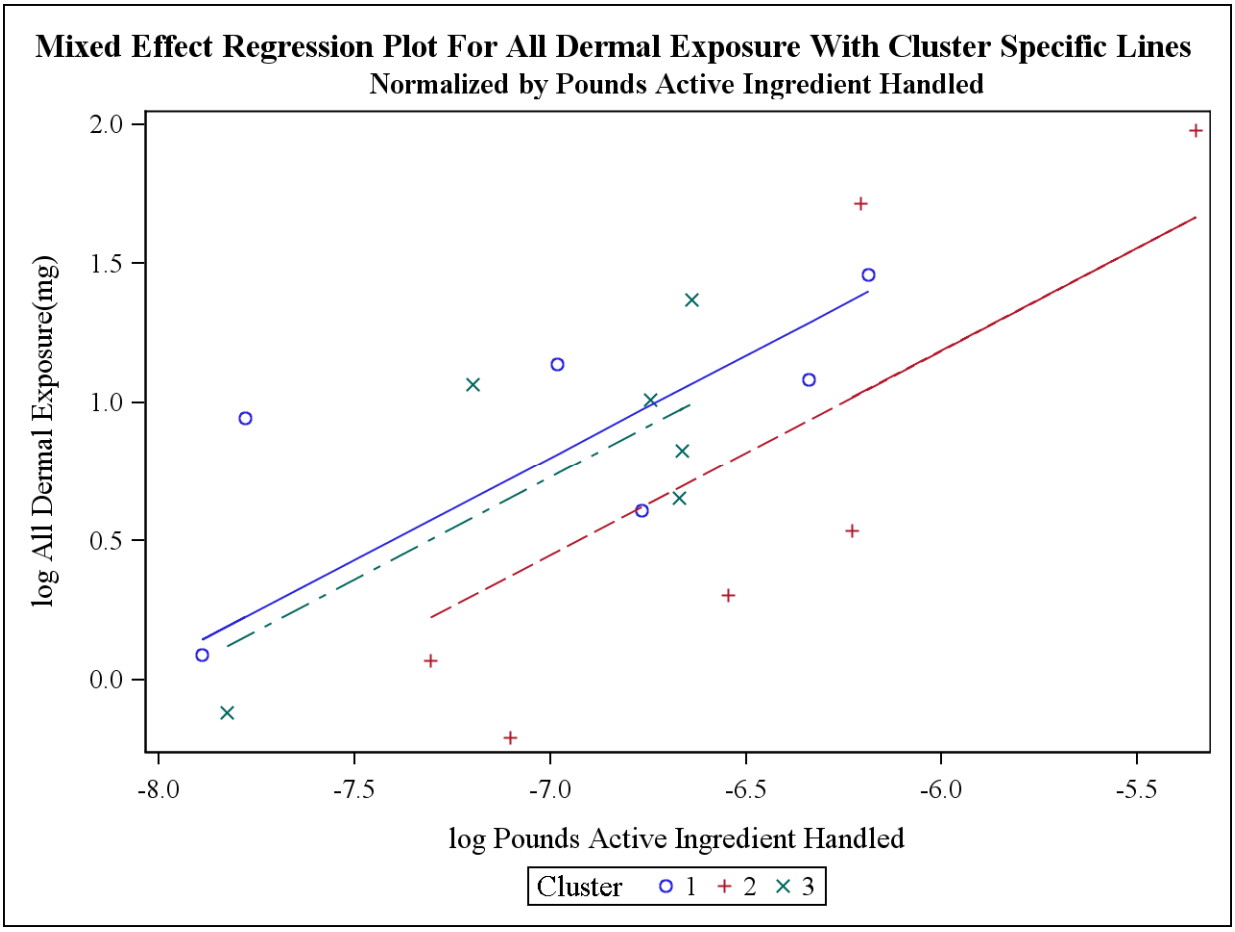

Figure 19

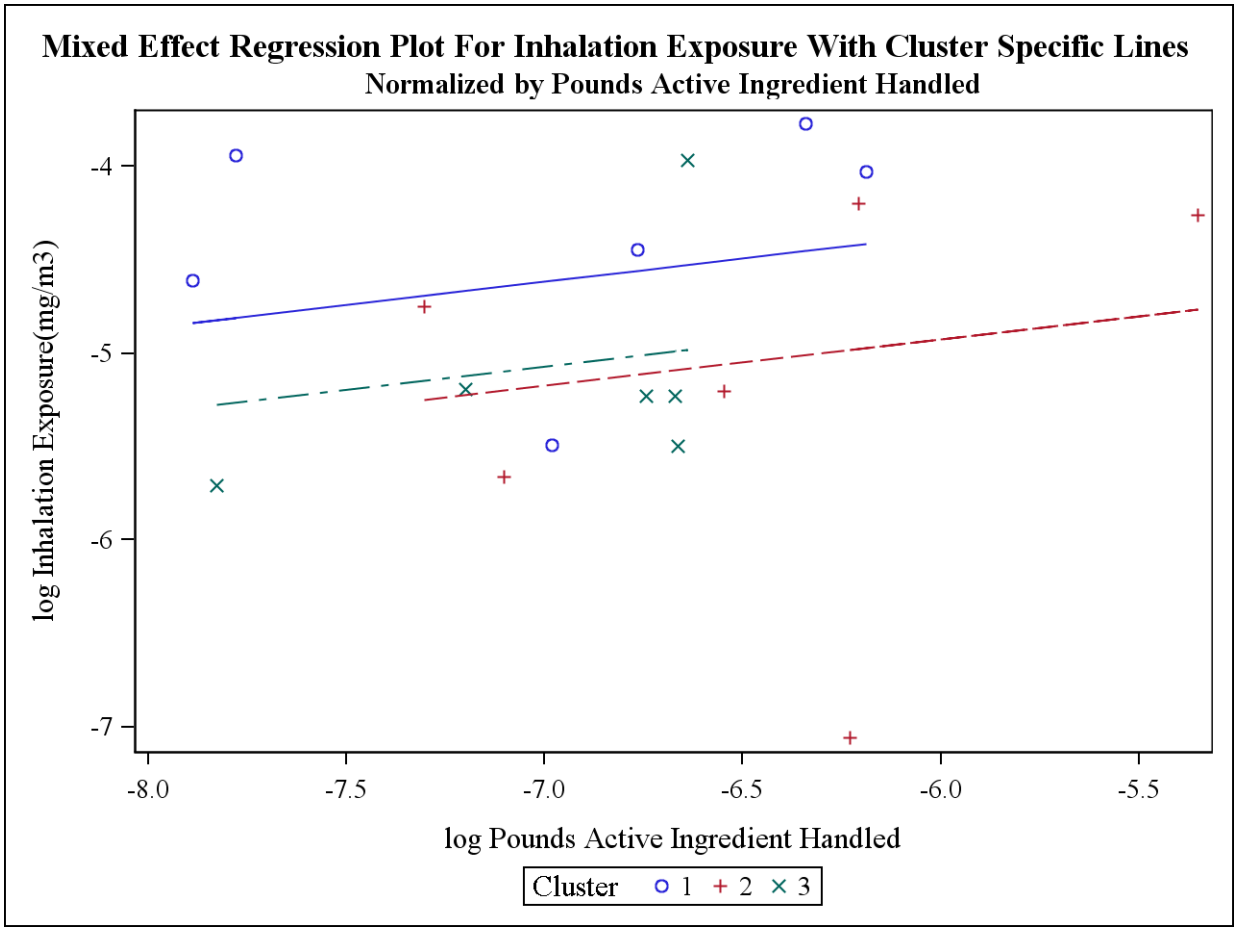

Figure 20

The above analyses of the proportionality for dermal exposure consistently show similar positive slopes, as one might expect on physical grounds. While all of the estimated slopes for dermal exposure are positive and approximately 0.5, the confidence intervals were inconsistent about whether they included zero or included one. To investigate this issue further, the following more complicated statistical model was fitted to the data of all three dermal exposures (excluding the unrealistic no clothing case) for all 18 subjects. The model was of the form:

Log (dermal exposure) = LnGM (clothing type) + Slope × Log (Pounds of Active Ingredient) + Cluster + Error

In this model, the intercept depends upon the clothing type, so there are three intercepts. The slope is the same for all three clothing types, The Cluster term accounts for possible clustering effects due to the location. Finally, to account for the expected correlations between different dermal exposure measurements on the same worker, the three error terms (one per clothing type) for each worker are assumed to be correlated (with an unspecified covariance matrix), but errors for different workers are assumed to be independent. Thus in SAS terminology, the Cluster effect is a RANDOM effect and the Error is a REPEATED effect where the subject is the worker. We will call this model the "Repeated Measures" model. The confidence interval for the slope using this statistical model is shown in the bottom row of Table 8. Since the confidence interval does not include one and does not include zero, the proportionality for dermal exposure has not been shown using this statistical model.

Quadratic models

The proportionality test was based on a linear model for log exposure versus log pounds active ingredient handled. The HSRB suggested that a quadratic model should also be considered.

There are two quadratic models that could be considered. Since the original linear model is of the form

$$\text{Log (Exposure)} = \text{Intercept} + \text{Slope} \times \text{Log (Pounds of Active Ingredient)} + \text{Error Terms},$$

the main quadratic model is of the form

$$\text{Log (Exposure)} = \text{Intercept} + \text{Slope} \times \text{Log (Pounds of Active Ingredient)} + \text{Quad} \times \{\text{Log (Pounds of Active Ingredient)}\}^2 + \text{Error Terms}.$$

Note that the quadratic term is the square of the logarithm of the pounds of active ingredient rather than the logarithm of the square; the latter approach produces an ill-defined model with two multiples of the logarithm of the pounds of active ingredient.

Another approach might be to consider a quadratic model for exposure:

$$\text{Exposure} = \text{Intercept} + \text{Slope} \times \text{(Pounds of Active Ingredient)} + \text{Quad} \times \text{(Pounds of Active Ingredient)}^2 + \text{Error Terms}.$$

We do not recommend this second approach for these data since the exposures are known to be non-negative and the quantile plots indicate that the exposure data are better modeled using a log-normal distribution than using a normal distribution. Furthermore, unless the intercept is zero, this model predicts a nonzero exposure when the pounds of active ingredient is zero, and so a more realistic (though possibly poorer-fitting) model of this form would have a zero intercept. For other exposure data a proportionality test could be carried out by fitting the zero intercept model

$$\text{Exposure} = \text{Slope} \times \text{(Pounds of Active Ingredient)} + \text{Quad} \times \text{(Pounds of Active Ingredient)}^2 + \text{Error Terms}$$

and testing if Quad equals zero.

The parsimony principle suggests that the appropriate statistical procedure for this study is to first fit the quadratic regression model for the logarithm of the exposure

$$\text{Log (Exposure)} = \text{Intercept} + \text{Slope} \times \text{Log (Pounds of Active Ingredient)} + \text{Quad} \times \{\text{Log (Pounds of Active Ingredient)}\}^2 + \text{Error Terms}.$$

If the coefficient Quad is statistically significant at the 5% level, which is equivalent to requiring that the 95% confidence interval does not include zero, than the quadratic model is supported. Otherwise the linear model should be used.

We will first present the results of fitting these quadratic models to the study data. We will then consider whether these statistical models produce meaningful and useful physical models for antimicrobial exposure.

Table 9 presents the fitted quadratic models from the study for the mixed models of the four exposure measurements (Long Dermal, Short Dermal, Long Short Dermal, Inhalation) and for the Repeated Measures model for Dermal exposures. For the Repeated Measures model, the model has different intercepts (but the same Slope and Quad coefficients) for the three different dermal exposures. In view of the earlier discussion about denominator degrees of freedom, the confidence intervals for cases where the ICC parameter is non-zero and for the Repeated Measures model are calculated using the Kenwood-Rogers method. The confidence intervals for other cases where the ICC parameter is zero are calculated using the containment method.

Table 9. Quadratic mixed models with 95% confidence intervals for the log exposure versus log pounds active ingredient handled.

Exposure	**Parameter**	**Estimate**	**Degrees of Freedom**	**Lower Bound**	**Upper Bound**	**GSD**	**ICC**	**Width of Confidence Interval**
Long Dermal	Intercept	9.80	2.00	-32.28	51.87	1.64	0.00	84.16
Long Dermal	Slope	2.55	13.00	-3.70	8.79	1.64	0.00	12.49
Long Dermal	Quad	0.16	13.00	-0.30	0.62	1.64	0.00	0.92
Short Dermal	Intercept	19.19	14.22	0.05	38.32	1.55	0.07	38.27
Short Dermal	Slope	4.94	14.09	-0.68	10.56	1.55	0.07	11.23
Short Dermal	Quad	0.32	13.96	-0.09	0.73	1.55	0.07	0.82
Long Short Dermal	Intercept	19.96	2.00	-18.23	58.15	1.57	0.00	76.37
Long Short Dermal	Slope	5.22	13.00	-0.44	10.89	1.57	0.00	11.34
Long Short	Quad	0.34	13.00	-0.07	0.76	1.57	0.00	0.83

Exposure	Parameter	Estimate	Degrees of Freedom	Lower Bound	Upper Bound	GSD	ICC	Width of Confidence Interval
Dermal								
Inhalation	Intercept	10.83	13.88	-25.31	46.98	2.44	0.19	72.29
Inhalation	Slope	4.42	13.79	-6.20	15.04	2.44	0.19	21.24
Inhalation	Quad	0.31	13.70	-0.47	1.08	2.44	0.19	1.55
Dermal Repeated Measures	Slope	4.29	13.30	-2.04	10.62	NA	NA	12.64
Dermal Repeated Measures	Quad	0.27	13.16	-0.19	0.74	NA	NA	0.93

Since the 95% confidence intervals for Quad include zero in every case, the quadratic coefficient is not statistically significant and the quadratic models are not supported.

Physical Implications

Let us now consider the physical implications of these quadratic models. Exponentiating both sides of the exposure regression equation (and assuming zero error) produces the model

Exposure = exp[Intercept + Slope × Log (Pounds of Active Ingredient) + Quad × {Log (Pounds of Active Ingredient)}^{2}}]

= A(Pounds of Active Ingredient)^{Slope} × exp[Quad × {Log (Pounds of Active Ingredient)}^{2}}]

where A = exp(Intercept). The final term does not simplify unless Quad equals zero.

Under the quadratic model, the predicted exposure will not double if the amount of active ingredient is doubled, which would happen if the same amounts of liquid were sprayed onto the rags but the concentration in the bottle is doubled, or if the duration is doubled and the concentration in each spray bottle is the same. In the first case, the physical model might be explained by some non-linearity in atmospheric or physical processes. In the second case, a physical explanation might be something like the idea that if you wipe for twice as long, you get more tired which increases the probability of larger accidental exposures, or alternatively that if you wipe twice as long, you get more experienced which decreases the probability of exposures. For the DDAC experiment the concentration in each bottle was the same (other than the unplanned slight concentration differences of 1/65 versus 1/64 between cluster 1 and clusters 2 and 3), so we only have data for the second case and cannot estimate what would happen in the first case without making additional assumptions. According to this logic, if the quadratic model is true then the results of the DDAC experiment could only be used directly to estimate exposures when the liquid concentration is the same as used in the experiment,

and you would need to make additional assumptions in order to use the same model to predict exposures when DDAC is used at a different concentration or, more importantly, when another antimicrobial is used instead of DDAC.

If Quad equals zero, then the model becomes the Linear model for log Exposure and the exposure equation becomes

$$\text{Exposure} = A(\text{Pounds of Active Ingredient})^{\text{Slope}}$$

Unless Slope = 1, the predicted exposure will not double if the amount of active ingredient is doubled, which again implies non-linearity in the exposure. However if Quad equals 0 and Slope = 1, then the exposure is proportional to the amount of active ingredient and the model implies that normalized exposure is physically meaningful, and hence that the results of the DDAC experiment can be used directly to estimate exposures when DDAC is used at a different concentration or, more importantly, when another antimicrobial is used instead of DDAC.

The primary goal of the analysis should be to test whether or not the exposures are proportional to the amount of active ingredient, rather than trying to find the best-fitting statistical model for the exposure as a function of the amount of active ingredient. The first step should be to use the Linear model for log Exposure for the proportionality test, which compares the proportionality model with the model $\text{Exposure} = A(\text{Pounds of Active Ingredient})^{\text{Slope}}$. If the proportionality is rejected, then the Quadratic model and other complicated model formulations could then be considered. However in this case it would be desirable to obtain exposure data using different liquid concentrations of DDAC and/or different antimicrobials to develop physically realistic models without making untested assumptions.

Over-prediction from normalized exposure model.

As an approximation, one can use the normalized exposure model to estimate exposures even if the proportionality assumption is rejected by the statistical test. Suppose that the linear model for log Exposure is correct. Then the exposure is given by the equation

$$\text{Exposure estimate from linear model} = \exp(\text{Intercept}) \times (\text{Pounds of Active Ingredient})^{\text{Slope}}$$

If the normalized exposure model is used to estimate the expected exposure, then the estimated exposure is given by the pounds of active ingredient multiplied by the average normalized exposure, which is estimated by AMm, the arithmetic mean from the lognormal mixed model. Thus we have

$$\text{Exposure estimate from normalized exposure model} = \text{AMm} \times \text{Pounds of Active Ingredient}$$

Suppose that the estimated slope is less than 1. Then the exposure estimate from the normalized exposure model will over-predict the exposure from the linear model if, and only if, the pounds of active ingredient exceeds the following threshold:

$$\text{Threshold} = \{\text{AMm} / \exp(\text{Intercept})\}^{1/(\text{Slope} - 1)}$$

These threshold values are given in Table 10.

Table 10. Minimum Pounds of Active Ingredient for Which Normalized Exposure Model Over-Predicts Dermal and Inhalation Exposure.

Exposure Route	**Clothing**	**Model**	**Slope**	**Threshold Level (lb AiaH)**
Dermal (mg)	Long pants and long sleeves	Mixed	0.37	0.00081
	Short pants and short sleeves	Mixed	0.57	0.00080
	Long pants and short sleeves	Mixed	0.58	0.00078
Inhalation (mg/m3)		Mixed	0.25	0.00053

Alternative normalizing variables

The appendix gives the tables and graphs with the detailed results of the analysis when the exposure is normalized by the wiping duration or, for inhalation exposure only, by the product of pounds of active ingredient handled and wiping duration or by surface area wiped. The long dermal and repeated measures exposure models are inconsistent with proportionality for the wiping duration. The short dermal, long dermal, and all dermal exposure models are consistent with proportionality for the wiping duration, but the confidence intervals are much wider than for the amount of active ingredient. The inhalation exposure models are inconsistent with proportionality for product of pounds of active ingredient handled and wiping duration and are only just consistent with proportionality for the surface area wiped (upper bound of 95% confidence interval is 1.00).

The appendix also gives the tables and graphs with the detailed results of the analysis when the inhalation exposure concentration is converted to an estimated mass, calculated as the average air concentration multiplied by the wiping duration (hours) and by an estimated 1 m^3/hour of air breathed in by someone doing light activity. This value estimates the mass of DDAC breathed in by each participant. However this is an approximation because actual breathing rates are not constant and will vary with the activity as well as the individual. Moreover, the air concentration was measured and averaged over the entire air pumping period, which includes the resting periods (breaks) as well as the wiping durations. The analysis shown in the appendix is for the mass normalized by the amount of active ingredient.

Using both normalizing variables (amount of active ingredient, wiping duration), the ICC value is either zero or is small (at most 0.2) for all three dermal routes, showing only a small amount of variability between the clusters, i.e., the locations. Using the four normalizing variables (amount of active ingredient, wiping duration, amount of active ingredient × wiping duration, number of wipes) the ICC value for normalized inhalation exposure (as a concentration) was non-zero and at most 0.3, also showing that the inhalation exposure does not vary very much between the clusters. For dermal exposure routes normalizing by wiping duration, the slope of 0 was rejected only for the all dermal

exposure, and the slope of one was rejected only for long dermal exposure and the repeated measures model. For inhalation exposure as a concentration, the confidence intervals for the slope included zero and excluded one when normalizing by amount of active ingredient, wiping duration, or amount of active ingredient × wiping duration, but included both zero and one when normalizing by the surface area wiped. The slope estimates for the inhalation exposure as a concentration were all small (below 0.3) and positive. For the inhalation exposure as a mass normalized by the amount of active ingredient, the ICC value was non-zero and the confidence interval for the slope included one and excluded zero.

Finally, to compare the four different normalizing variables, we present Table 11 that gives the values of minus twice the log-likelihood "-2LL" for the alternative approaches and exposure routes. -2LL is a measure of how well a statistical model fits the data and this can be used to compare different models for the same data. (-2LL is a relative measure that can only be used to compare different models for the same data, such as the various models for the 18 long dermal exposure values. -2LL cannot be used to compare different data such as the long dermal and short dermal exposure). Using this measure, the models with the lowest -2LL values are preferred, and the preferred models in each row are shown in bold in Table 11. The values in Table 11 are -2LL for each of the mixed and repeated measures models. The log-likelihood values were computed by fitting the models using the maximum likelihood method. The rows where the slope is 1 give the -2LL values for the models where the regression slope is set to be 1 so the exposure is normalized by dividing the exposure by the normalizing variable. The rows where the slope = "Any" give the -2LL values for the more general models where the regression slope is arbitrary so the exposure is normalized by dividing the exposure by some power of the normalizing variable, NRM^p. The mixed models using the pounds of active ingredient are the preferred models for all the dermal exposure routes except for the long dermal model with a known slope of one. For inhalation exposure, the preferred model for normalized exposure as a concentration uses the surface area wiped. The preferred model for normalized inhalation exposure as a mass uses the surface area wiped when the slope is allowed to vary and uses the pounds of active ingredient when the slope equals one.

Table 11. Minus twice the log-likelihood for different mixed models (smaller is better). Preferred model is shown in bold.

Exposure Route	Model	Slope	Normalized by pounds of active ingredient	Normalized by wiping duration	Normalized by pounds of active ingredient and wiping duration	Normalized by surface area wiped
Long Dermal	Mixed	Any	**23.3**	26.0		
	Mixed	1	33.2	**31.8**		
Short Dermal	Mixed	Any	**20.6**	27.1		
	Mixed	1	**26.5**	30.4		
Long Short Dermal	Mixed	Any	**22.5**	29.1		
	Mixed	1	**27.8**	32.2		
Dermal	Repeated Measures	Any	**-2.6**	1.1		
		1	**4.5**	6.7		

Exposure Route	Model	Slope	Normalized by pounds of active ingredient	Normalized by wiping duration	Normalized by pounds of active ingredient and wiping duration	Normalized by surface area wiped
Inhalation Concentration (mg/m^3)	Mixed	Any	43.3	43.7	43.6	**42.1**
	Mixed	1	49.1	48.5	60.0	**47.3**
Inhalation Mass (mg)	Mixed	Any	41.8	43.7	42.3	**41.7**
	Mixed	1	**41.9**	43.7	49.1	42.4

APPENDIX

Analyses of exposure per wiping duration (hours)

Table and Figure Numbers are consistent with the main text (add "b").

Table 1b. Summary statistics for normalized exposure.

Statistic	Normalized Long[a] Dermal (mg/hour)	Normalized Short[b] Dermal (mg/hour)	Normalized Long Short[c] Dermal (mg/hour)	Normalized Inhalation (mg/m^3/hour)
Arithmetic Mean	0.62	1.06	0.95	0.0056
Arithmetic Standard Deviation	0.45	0.65	0.62	0.0050
Geometric Mean	0.51	0.90	0.79	0.0040
Geometric Standard Deviation	1.83	1.79	1.84	2.61
Min	0.25	0.39	0.38	0.0002
5%	0.25	0.39	0.38	0.0002
10%	0.27	0.49	0.39	0.0016
25%	0.32	0.56	0.46	0.0027
50%	0.40	0.82	0.69	0.0048
75%	0.76	1.79	1.30	0.0079
90%	1.66	2.07	1.97	0.0086
95%	1.71	2.54	2.39	0.0228
Max	1.71	2.54	2.39	0.0228

[a]Long = Long pants and long sleeves
[b]Short = Short pants and short sleeves
[c]Long Short = Long pants and short sleeves

Table 2b. Arithmetic mean and 95th percentile estimates from lognormal mixed model for normalized exposure.

Exposure Route	Clothing	Arithmetic Mean (95% confidence interval)	95th percentile (95% confidence interval)
Dermal (mg/hour)	Long pants and long sleeves	0.61 (0.45, 0.84)	1.38 (0.89, 2.12)
	Short pants and short sleeves	1.06 (0.80, 1.43)	2.32 (1.53, 3.53)
	Long pants and short sleeves	0.95 (0.70, 1.31)	2.15 (1.38, 3.33)
Inhalation (mg/m^3/hour)		0.0064 (0.0034, 0.0128)	0.0198 (0.0087, 0.0443)

Table 3b. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized long dermal exposure (mg/hour).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.83	1.50	2.23	1.2	1.50	1.99	1.2
GSDm	1.83	1.50	2.26	1.2	1.54	2.05	1.2
ICC	0.00	0.00	0.39		0.00	0.57	
GMs	0.51	0.39	0.68	1.3	0.39	0.68	1.3
GMm	0.51	0.39	0.68	1.3	0.39	0.68	1.3
AMs	0.62	0.45	0.83	1.4	0.44	0.82	1.4
AMu	0.61	0.45	0.84	1.4	0.43	0.84	1.4
AMm	0.61	0.45	0.84	1.4	0.44	0.85	1.4
P95s	1.71	0.88	3.05	1.9	0.82	1.71	2.1
P95u	1.38	0.88	2.09	1.6	0.78	1.98	1.8
P95m	1.38	0.89	2.12	1.5	0.81	2.02	1.7

Table 4b. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized short dermal exposure (mg/hour).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.79	1.47	2.17	1.2	1.52	1.96	1.2
GSDm	1.79	1.48	2.19	1.2	1.52	2.00	1.2
ICC	0.00	0.00	0.39		0.00	0.47	
GMs	0.90	0.69	1.18	1.3	0.70	1.16	1.3
GMm	0.90	0.69	1.18	1.3	0.70	1.16	1.3
AMs	1.06	0.79	1.41	1.3	0.78	1.36	1.4
AMu	1.06	0.79	1.43	1.3	0.77	1.39	1.4
AMm	1.06	0.80	1.43	1.4	0.78	1.41	1.4
P95s	2.54	1.52	5.00	2.0	1.81	2.54	1.4
P95u	2.32	1.52	3.48	1.5	1.45	3.19	1.6
P95m	2.32	1.53	3.53	1.5	1.46	3.27	1.6

Table 5b. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized long short dermal exposure (mg/hour).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	1.84	1.50	2.26	1.2	1.55	2.02	1.2
GSDm	1.84	1.51	2.28	1.2	1.56	2.06	1.2
ICC	0.00	0.00	0.39		0.00	0.43	
GMs	0.79	0.59	1.05	1.3	0.60	1.04	1.3
GMm	0.79	0.59	1.05	1.3	0.60	1.04	1.3
AMs	0.95	0.69	1.28	1.4	0.69	1.23	1.4
AMu	0.95	0.70	1.30	1.4	0.68	1.26	1.4
AMm	0.95	0.70	1.31	1.4	0.68	1.28	1.4
P95s	2.39	1.37	4.80	2.0	1.67	2.39	1.4
P95u	2.15	1.37	3.28	1.6	1.30	2.98	1.6
P95m	2.15	1.38	3.33	1.6	1.31	3.06	1.6

Table 6b. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation exposure (mg/m^3/hour).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDs	2.61	1.89	3.62	1.4	1.64	3.78	1.6
GSDm	2.65	1.90	3.80	1.4	1.65	4.16	1.6
ICC	0.12	0.00	0.56		0.00	0.60	
GMs	0.0040	0.0022	0.0071	1.8	0.0026	0.0057	1.5
GMm	0.0040	0.0022	0.0071	1.8	0.0026	0.0057	1.5
AMs	0.0056	0.0032	0.0118	2.1	0.0038	0.0078	1.5
AMu	0.0063	0.0033	0.0123	2.0	0.0043	0.0090	1.5
AMm	0.0064	0.0034	0.0128	2.0	0.0043	0.0100	1.6
P95s	0.0228	0.0086	0.0744	3.3	0.0083	0.0228	2.8
P95u	0.0192	0.0086	0.0418	2.2	0.0095	0.0319	2.0
P95m	0.0198	0.0087	0.0443	2.3	0.0097	0.0363	2.0

Table 8b. 95 percent confidence intervals for slope of log exposure versus log hours of wiping duration.

Exposure Route	Clothing	Model	Estimate	Lower	Upper	Confidence Interval Width
Dermal (mg)	Long pants and long sleeves	Mixed	0.32	-0.26	0.91	1.17
		Simple Linear	0.32	-0.26	0.90	1.16
	Short pants and short sleeves	Mixed	0.49	-0.11	1.10	1.21
		Simple Linear	0.49	-0.10	1.09	1.20
	Long pants and short sleeves	Mixed	0.48	-0.16	1.12	1.28
		Simple Linear	0.48	-0.15	1.11	1.26
	None	Mixed	0.63	0.001	1.26	1.26
		Simple Linear	0.63	0.008	1.25	1.24
Inhalation (mg/m^3/hour)		Mixed	0.04	-0.89	0.98	1.87
		Simple Linear	0.02	-0.94	0.97	1.90
Dermal (mg)	Any	Repeated Measures	0.38	-0.21	0.97	1.18

Table 9b. Quadratic mixed models with 95% confidence intervals for the log exposure versus log hours wiping duration.

Exposure	Parameter	Estimate	Degrees of Freedom	Lower Bound	Upper Bound	GSD	ICC	Width of Confidence Interval
Long Dermal	Intercept	-0.24	2.00	-1.23	0.74	1.72	0.00	1.97
Long Dermal	Slope	0.24	13.00	-1.79	2.28	1.72	0.00	4.08
Long	Quad	0.07	13.00	-1.72	1.86	1.72	0.00	3.57

Exposure	Parameter	Estimate	Degrees of Freedom	Lower Bound	Upper Bound	GSD	ICC	Width of Confidence Interval
Dermal								
Short Dermal	Intercept	0.24	2.00	-0.77	1.25	1.75	0.00	2.02
Short Dermal	Slope	0.05	13.00	-2.04	2.15	1.75	0.00	4.18
Short Dermal	Quad	0.40	13.00	-1.43	2.24	1.75	0.00	3.66
Long Short Dermal	Intercept	0.12	2.00	-0.95	1.19	1.81	0.00	2.14
Long Short Dermal	Slope	0.10	13.00	-2.11	2.31	1.81	0.00	4.43
Long Short Dermal	Quad	0.35	13.00	-1.59	2.29	1.81	0.00	3.88
Inhalation	Intercept	-4.94	8.03	-5.87	-4.02	2.47	0.11	1.86
Inhalation	Slope	0.23	13.14	-2.99	3.45	2.47	0.11	6.45
Inhalation	Quad	-0.17	13.13	-3.00	2.65	2.47	0.11	5.64
Dermal Repeated Measures	Slope	0.13	15.01	-1.92	2.19	NA	NA	4.11
Dermal Repeated Measures	Quad	0.23	15.01	-1.57	2.03	NA	NA	3.60

Table 10b. Minimum Hours Wiping Duration for Which Normalized Exposure Model Over-Predicts Dermal and Inhalation Exposure.

Exposure Route	**Clothing**	**Model**	**Slope**	**Threshold Level (hours)**
Dermal (mg)	Long pants and long sleeves	Mixed	0.32	1.4
	Short pants and short sleeves	Mixed	0.49	1.3
	Long pants and short sleeves	Mixed	0.48	1.3
Inhalation (mg/m3)		Mixed	0.04	1.1

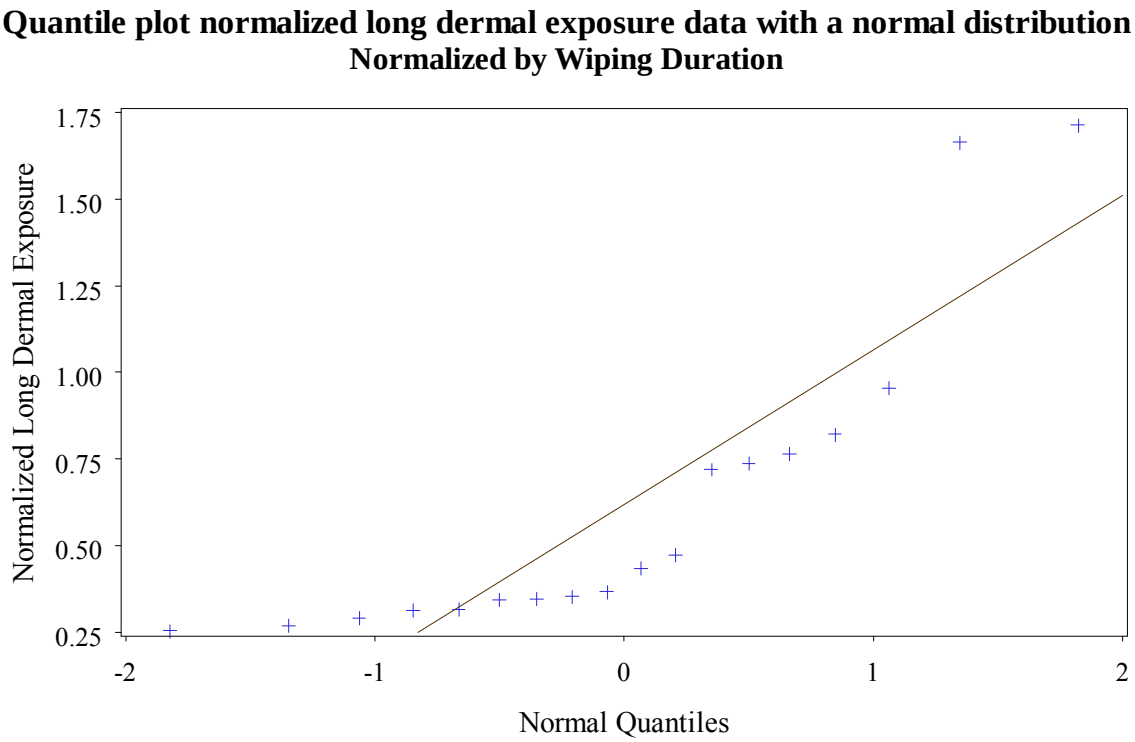
Quantile plot normalized long dermal exposure data with a normal distribution
Normalized by Wiping Duration
Normalized Long Dermal Exposure
1.75
1.50
1.25
1.00
0.75
0.50
0.25
-2
-1
0
1
2
Normal Quantiles

Figure 1b

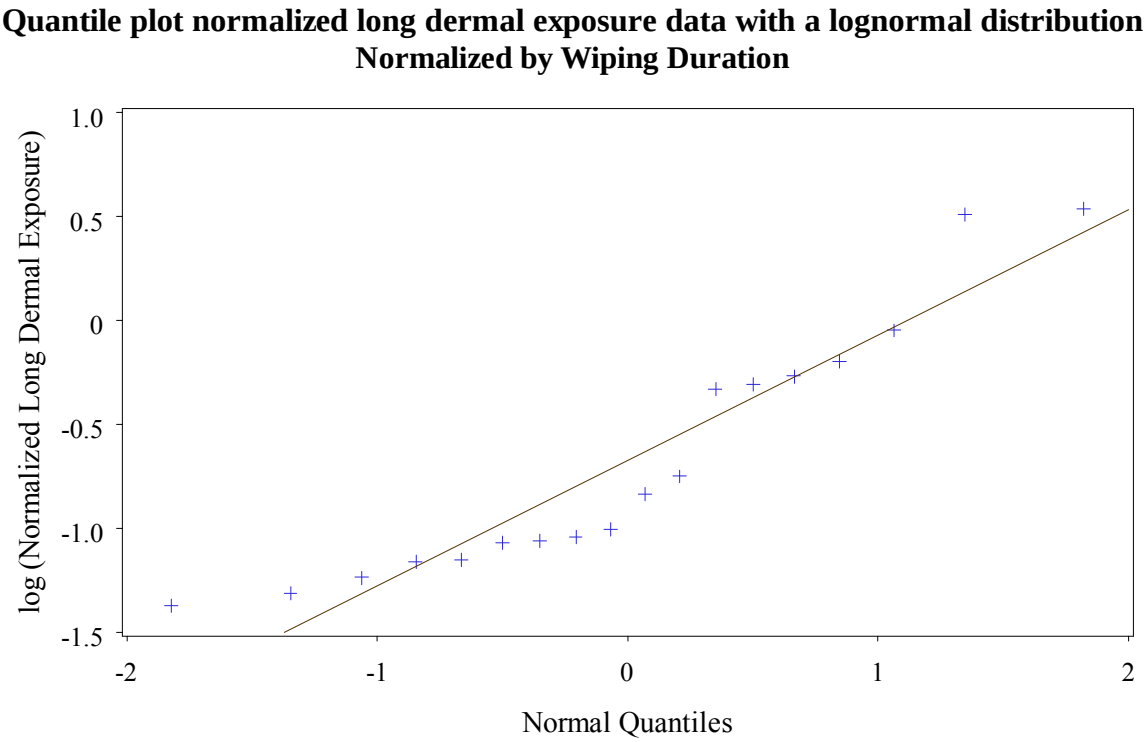
Quantile plot normalized long dermal exposure data with a lognormal distribution
Normalized by Wiping Duration
log (Normalized Long Dermal Exposure)
1.0
0.5
0
-0.5
-1.0
-1.5
-2
-1
0
1
2
Normal Quantiles

Figure 2b

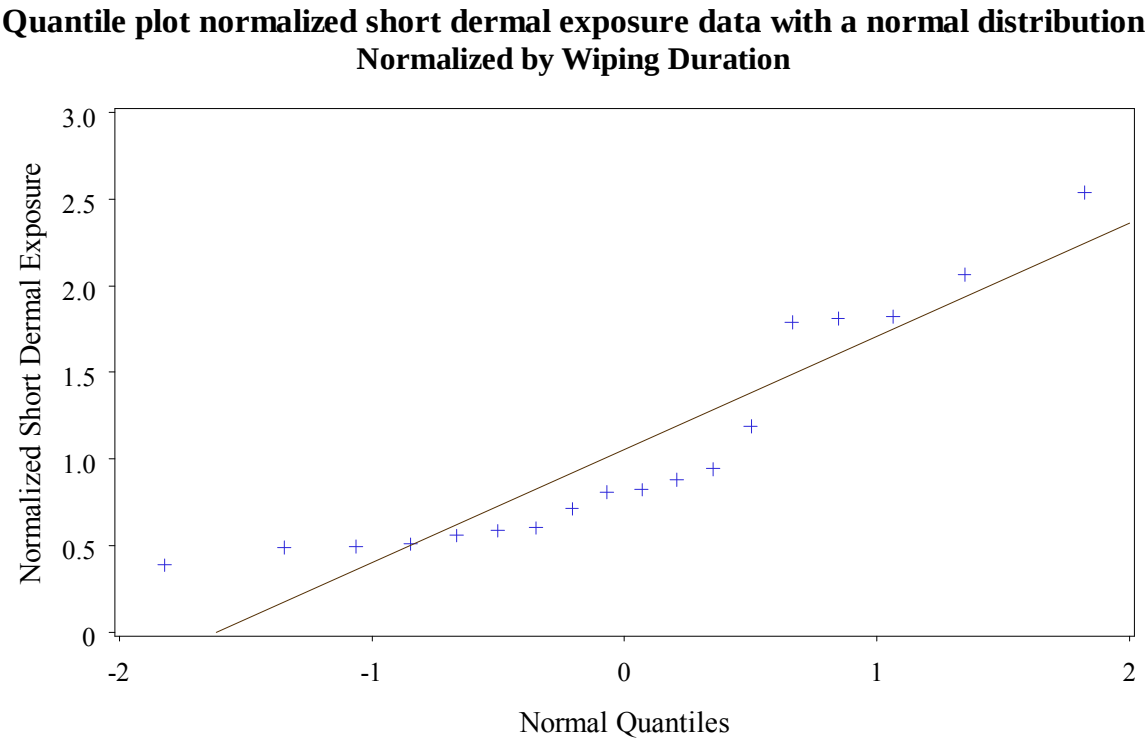
Quantile plot normalized short dermal exposure data with a normal distribution
Normalized by Wiping Duration
Normalized Short Dermal Exposure
3.0
2.5
2.0
1.5
1.0
0.5
0
-2
-1
0
1
2
Normal Quantiles

Figure 3b

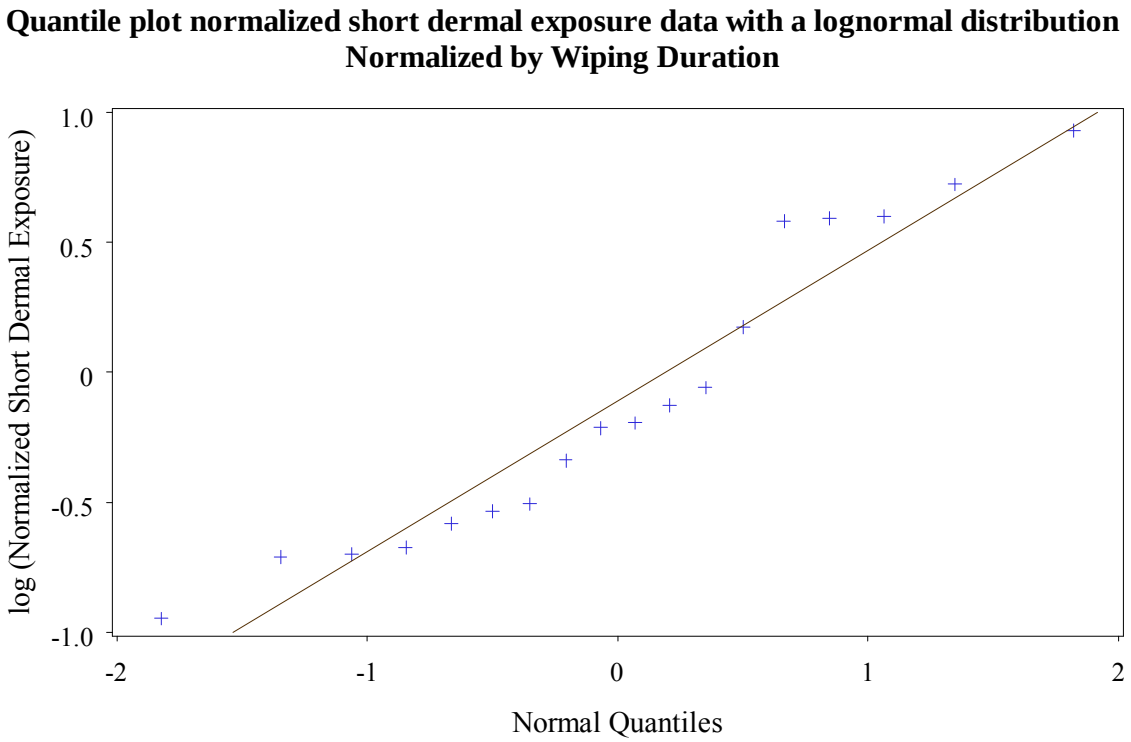
Quantile plot normalized short dermal exposure data with a lognormal distribution
Normalized by Wiping Duration
log (Normalized Short Dermal Exposure)
1.0
0.5
0
-0.5
-1.0
-2
-1
0
1
2
Normal Quantiles

Figure 4b

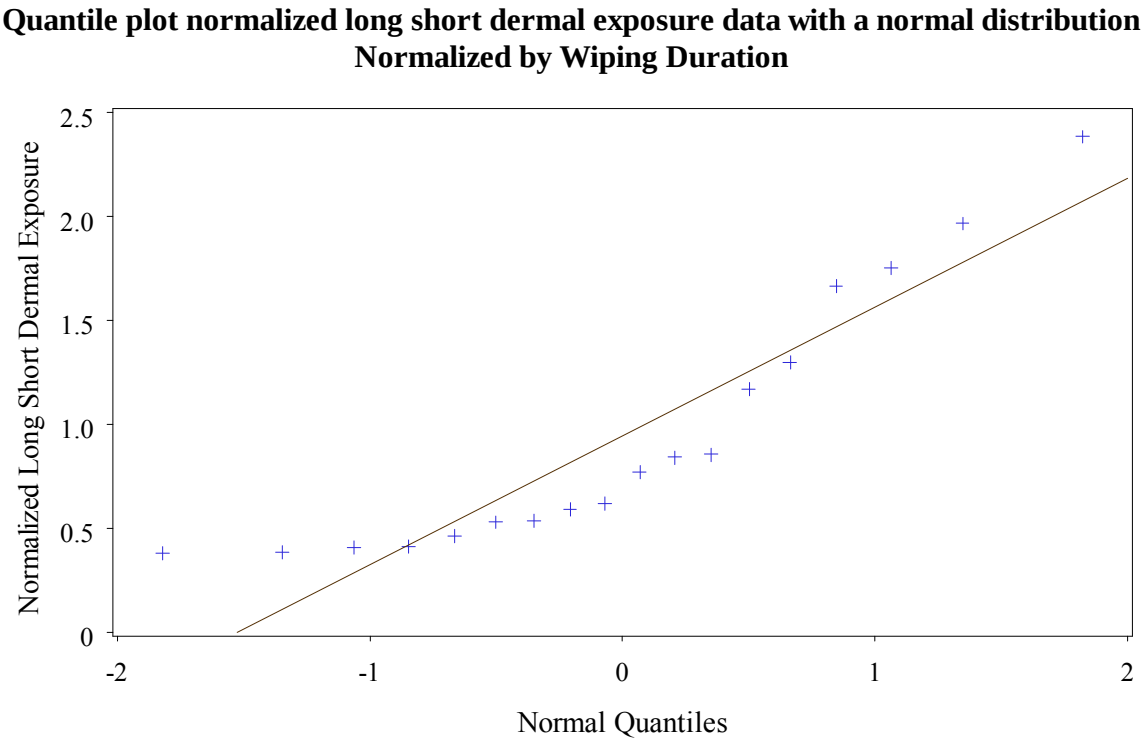
Quantile plot normalized long short dermal exposure data with a normal distribution
Normalized by Wiping Duration
Normalized Long Short Dermal Exposure
2.5
2.0
1.5
1.0
0.5
0
-2
-1
0
1
2
Normal Quantiles

Figure 5b

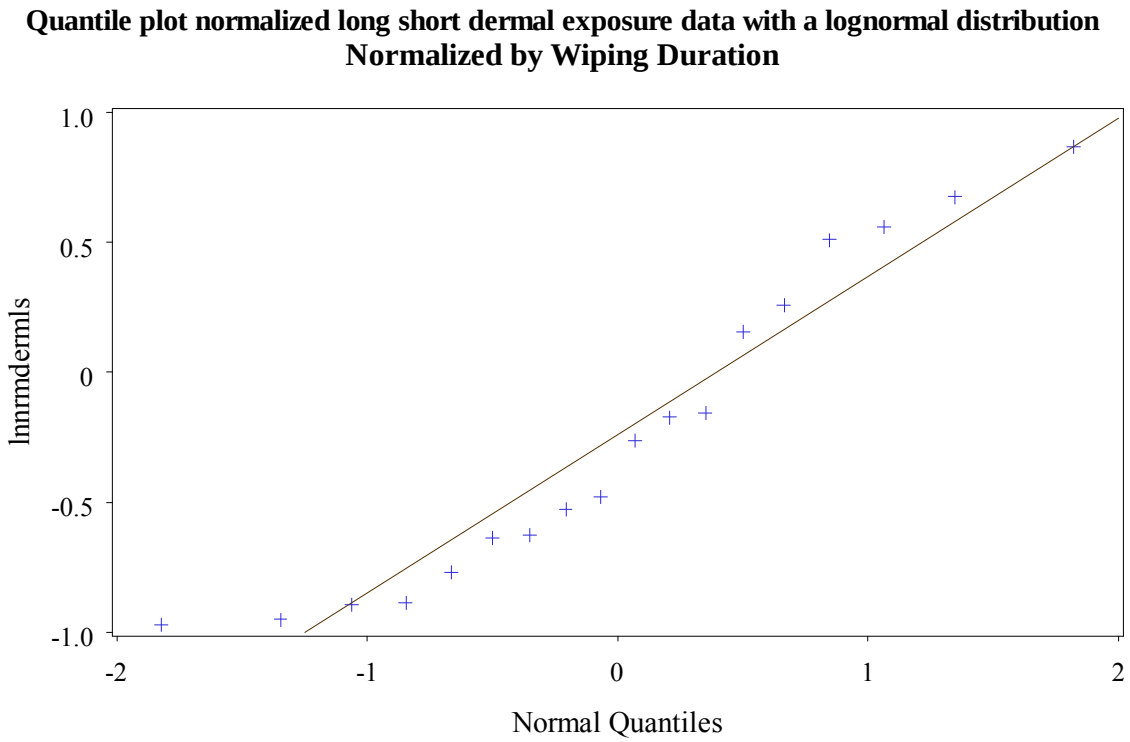
Quantile plot normalized long short dermal exposure data with a lognormal distribution
Normalized by Wiping Duration
lnnrmdermls
1.0
0.5
0
-0.5
-1.0
-2
-1
0
1
2
Normal Quantiles

Figure 6b

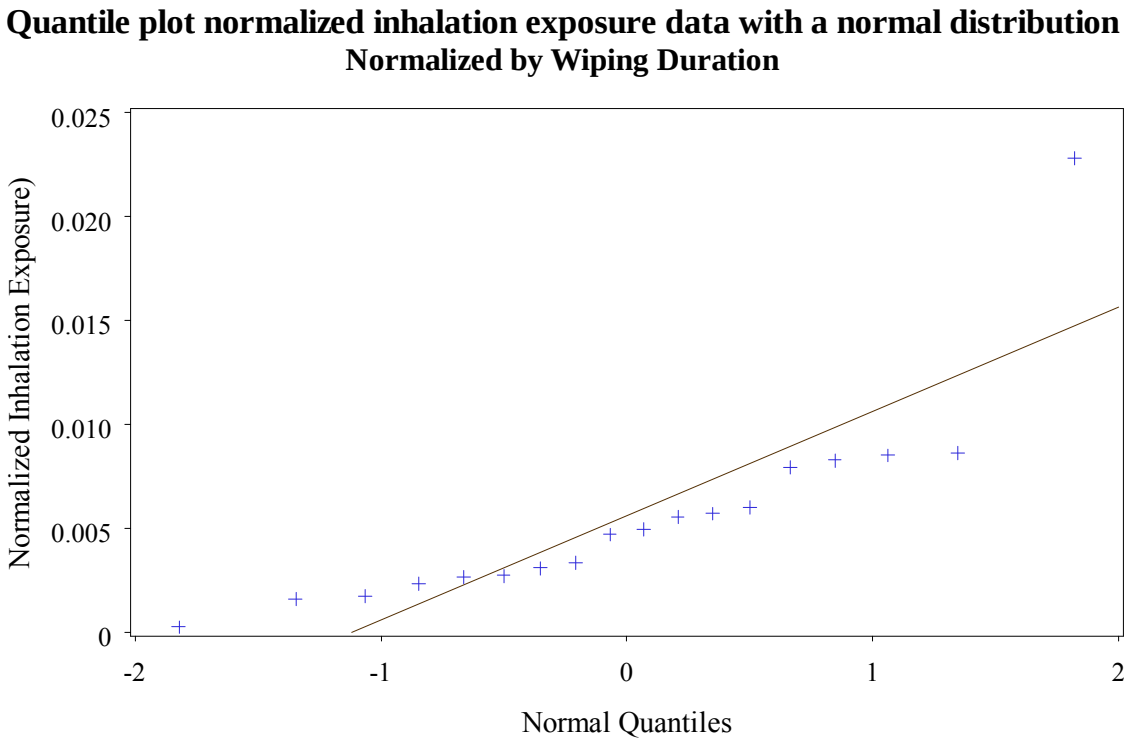
Quantile plot normalized inhalation exposure data with a normal distribution
Normalized by Wiping Duration
Normalized Inhalation Exposure)
0.025
0.020
0.015
0.010
0.005
0
-2
-1
0
1
2
Normal Quantiles

Figure 7b

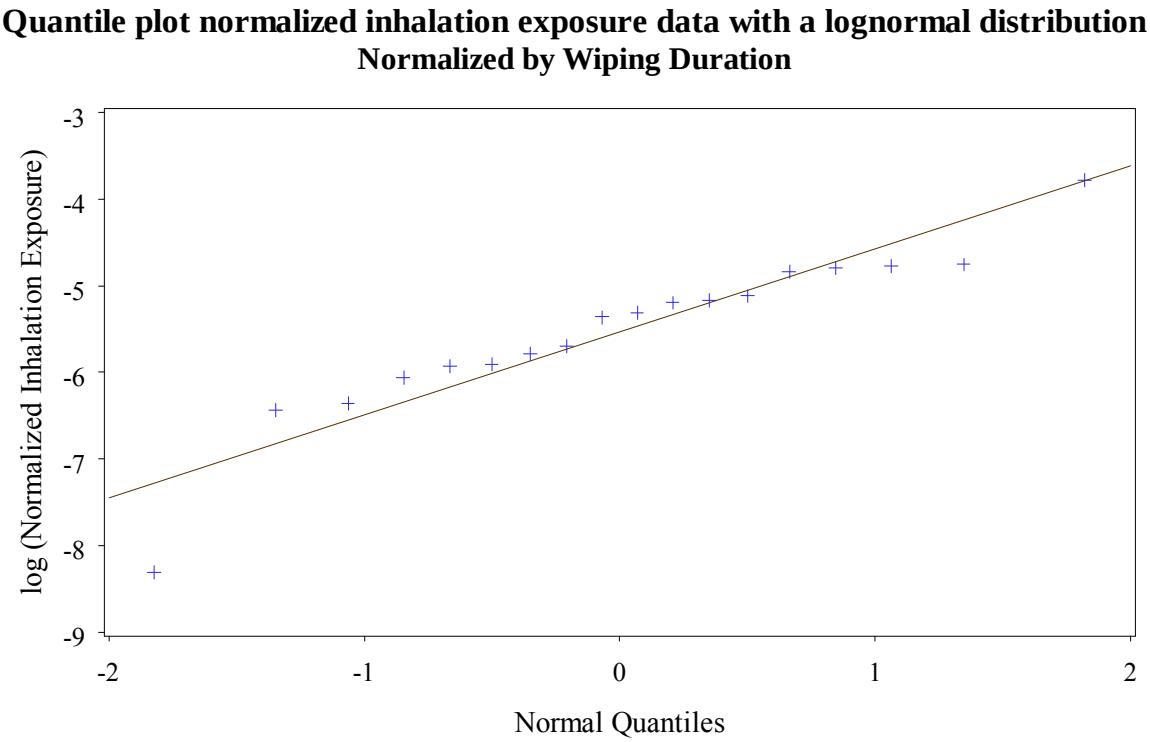
Quantile plot normalized inhalation exposure data with a lognormal distribution
Normalized by Wiping Duration
log (Normalized Inhalation Exposure)
-3
-4
-5
-6
-7
-8
-9
-2
-1
0
1
2
Normal Quantiles

Figure 8b

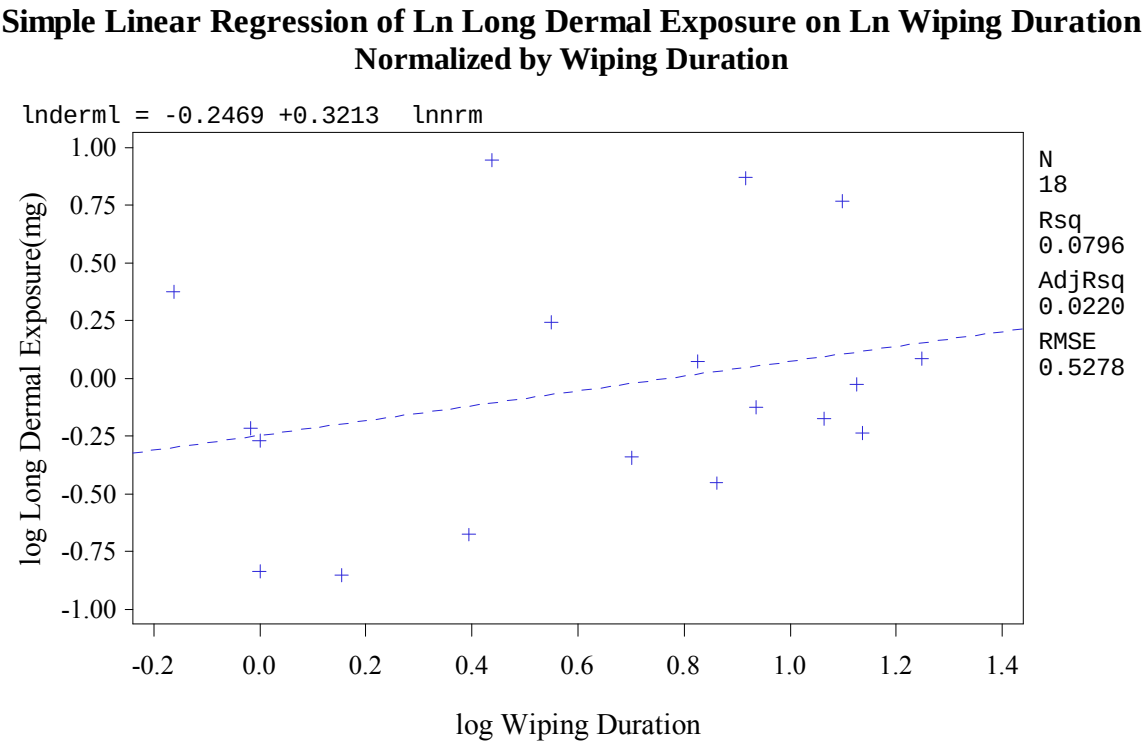
Simple Linear Regression of Ln Long Dermal Exposure on Ln Wiping Duration
Normalized by Wiping Duration
lnderml = -0.2469 +0.3213 lnnrm
N
18
Rsq
0.0796
AdjRsq
0.0220
RMSE
0.5278
log Long Dermal Exposure(mg)
1.00
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
log Wiping Duration

Figure 9b

Simple Linear Regression of Ln Short Dermal Exposure on Ln Wiping Duration Normalized by Wiping Duration

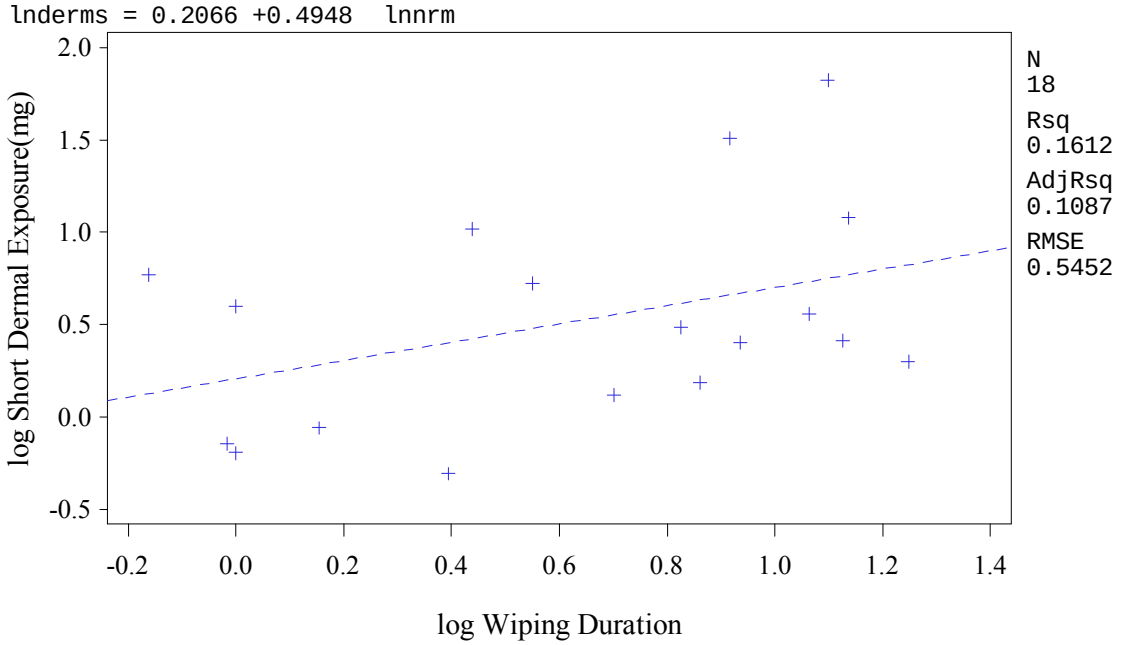

Figure 10b

Simple Linear Regression of Ln Long Short Dermal Exposure on Ln Wiping Duration Normalized by Wiping Duration

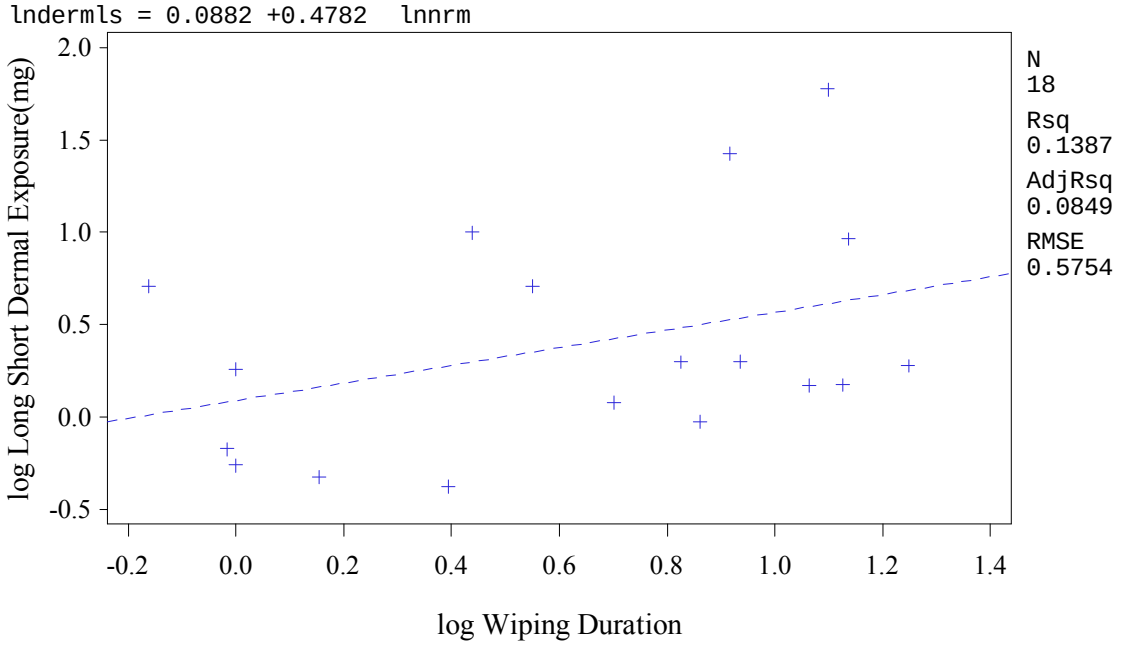

Figure 11b

Simple Linear Regression of Ln All Dermal Exposure on Ln Wiping Duration
Normalized by Wiping Duration

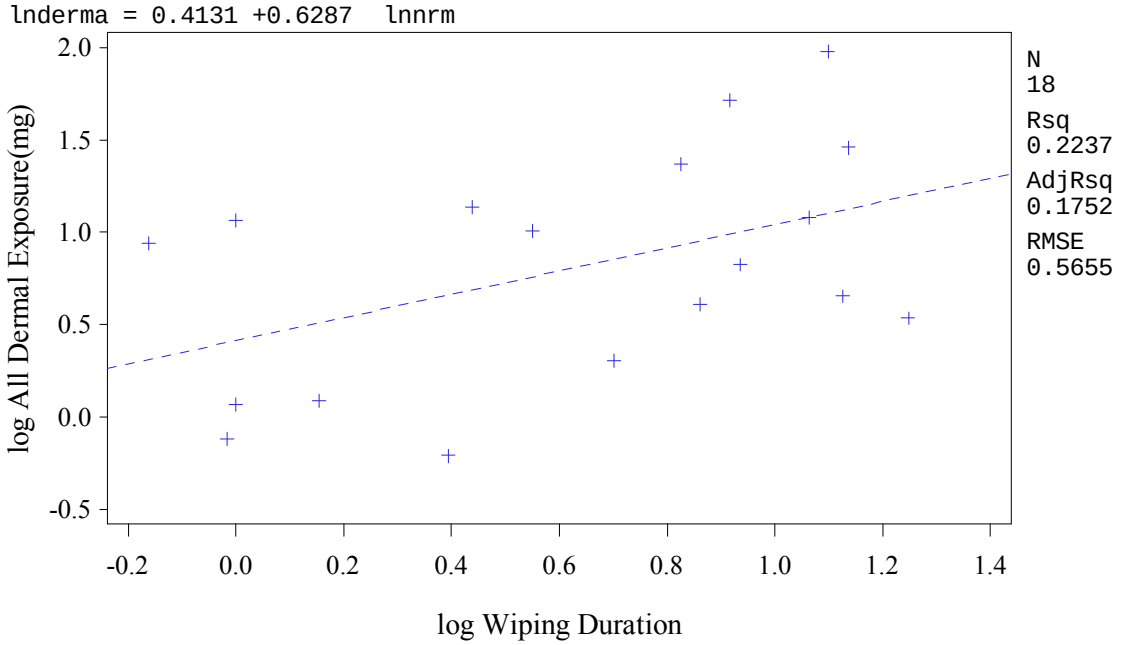

Figure 12b

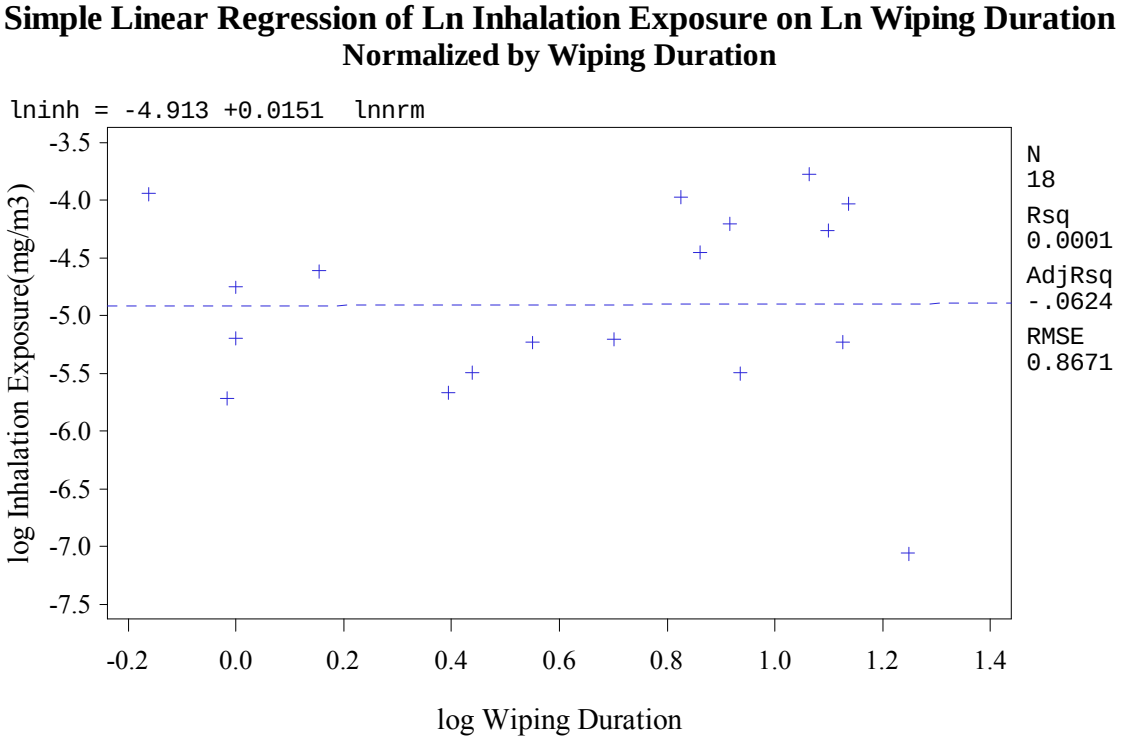
Simple Linear Regression of Ln Inhalation Exposure on Ln Wiping Duration
Normalized by Wiping Duration
lninh = -4.913 +0.0151 lnnrm
log Inhalation Exposure(mg/m3)
-3.5
-4.0
-4.5
-5.0
-5.5
-6.0
-6.5
-7.0
-7.5
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
log Wiping Duration
N
18
Rsq
0.0001
AdjRsq
-.0624
RMSE
0.8671

Figure 13b

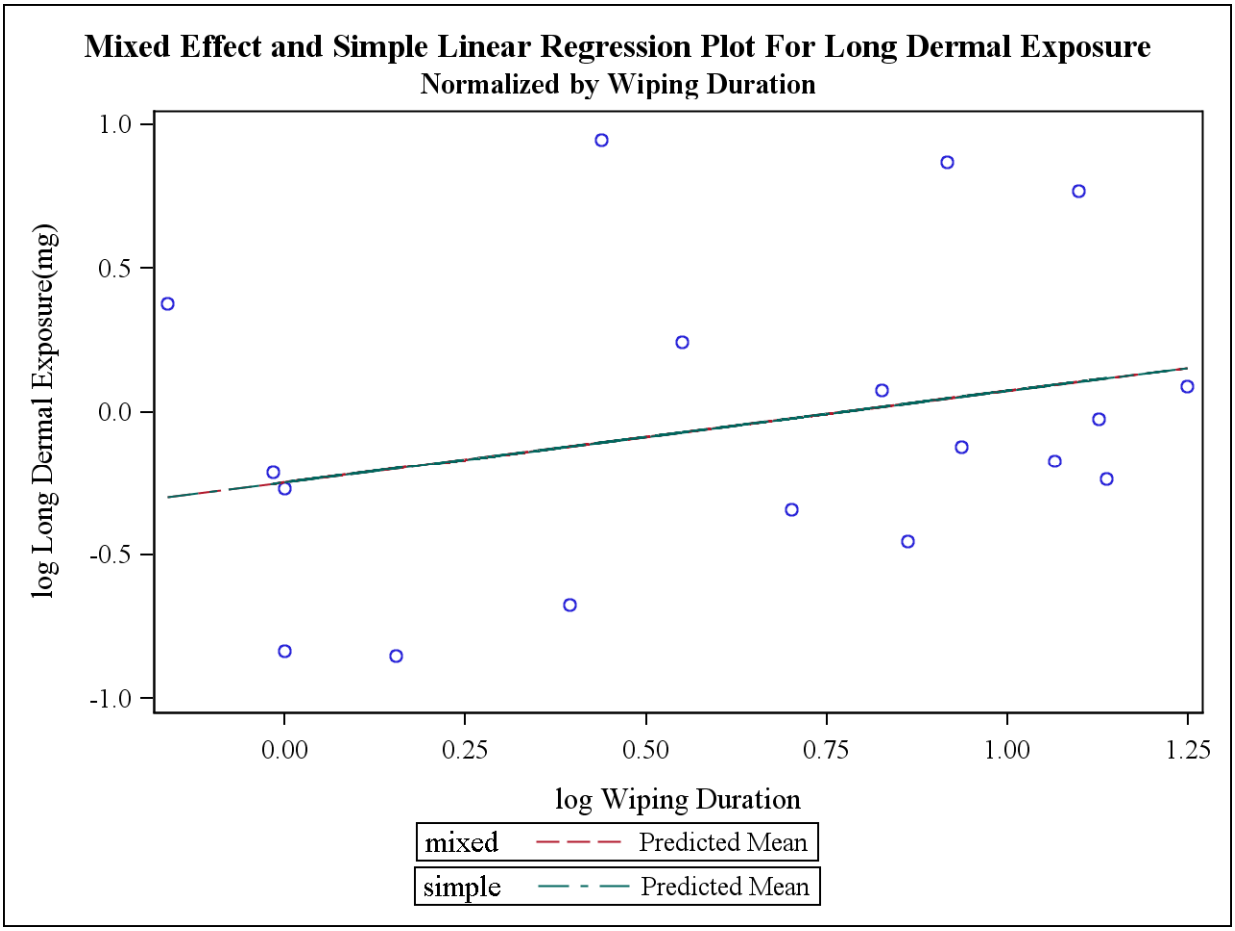
Mixed Effect and Simple Linear Regression Plot For Long Dermal Exposure
Normalized by Wiping Duration
log Long Dermal Exposure(mg)
1.0
0.5
0.0
-0.5
-1.0
0.00
0.25
0.50
0.75
1.00
1.25
log Wiping Duration
mixed Predicted Mean
simple Predicted Mean

Figure 14b

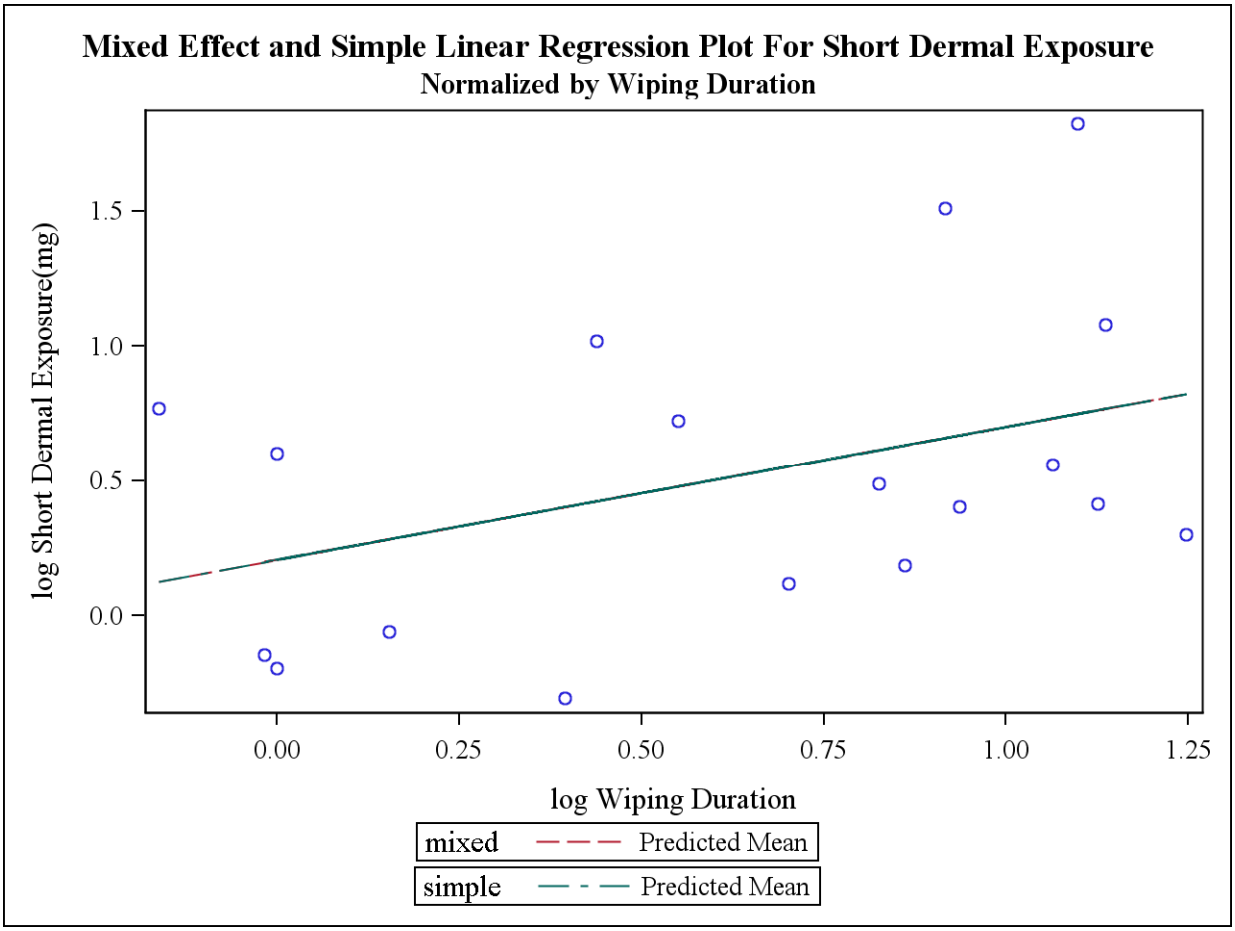
Mixed Effect and Simple Linear Regression Plot For Short Dermal Exposure
Normalized by Wiping Duration
log Short Dermal Exposure(mg)
1.5
1.0
0.5
0.0
0.00
0.25
0.50
0.75
1.00
1.25
log Wiping Duration
mixed Predicted Mean
simple Predicted Mean

Figure 15b

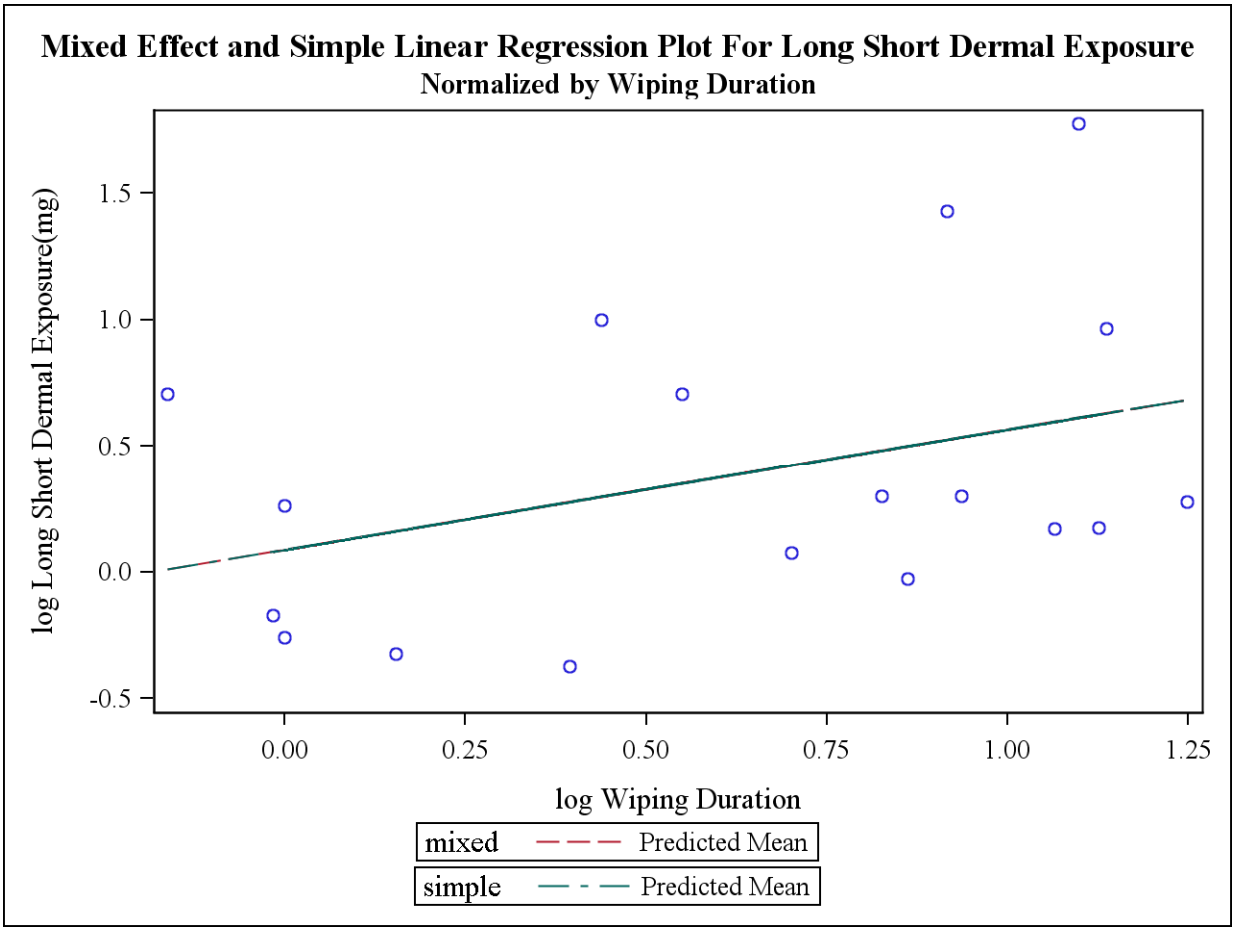
Mixed Effect and Simple Linear Regression Plot For Long Short Dermal Exposure
Normalized by Wiping Duration
log Long Short Dermal Exposure(mg)
1.5
1.0
0.5
0.0
-0.5
0.00
0.25
0.50
0.75
1.00
1.25
log Wiping Duration
mixed
Predicted Mean
simple
Predicted Mean

Figure 16b

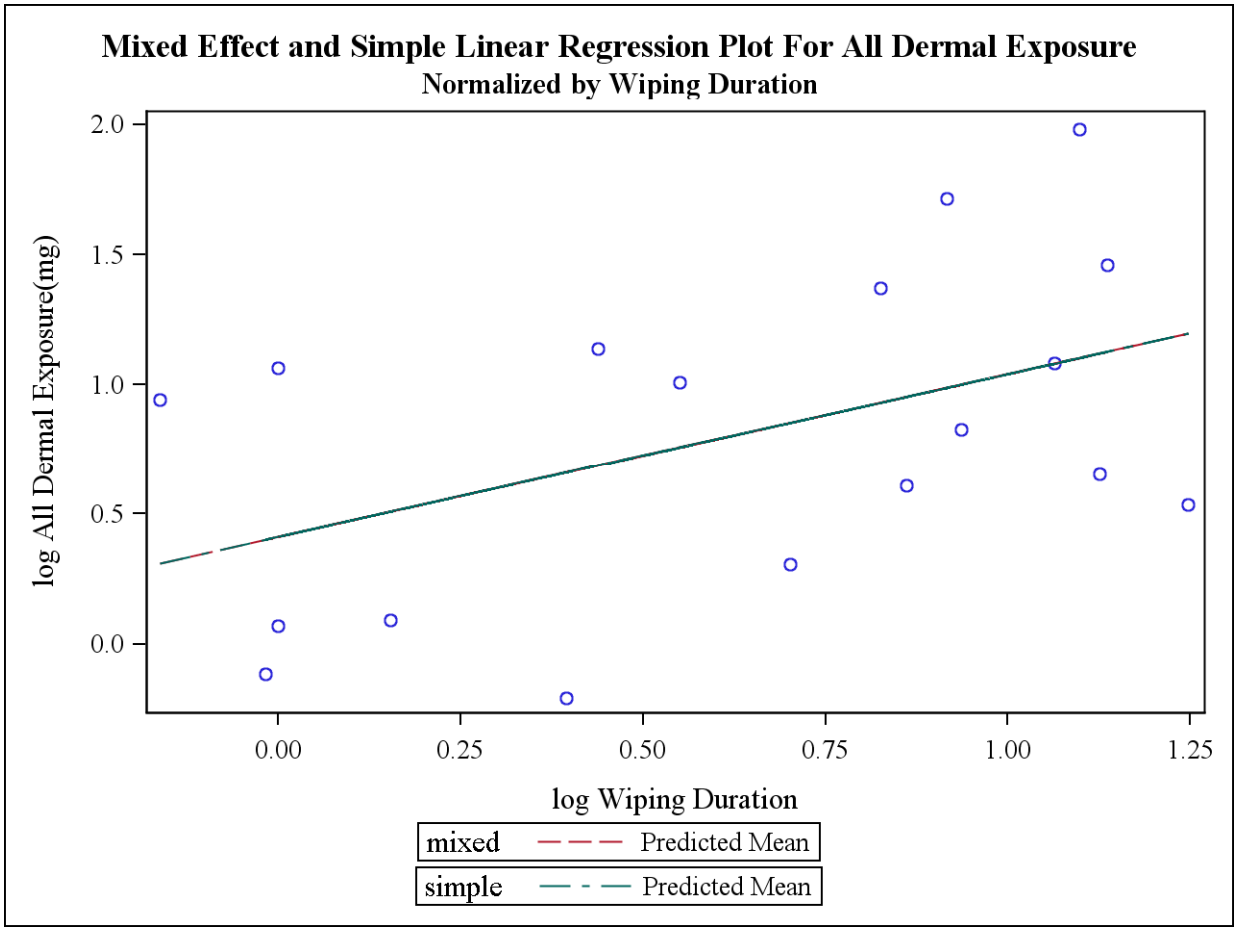
Mixed Effect and Simple Linear Regression Plot For All Dermal Exposure
Normalized by Wiping Duration
log All Dermal Exposure(mg)
2.0
1.5
1.0
0.5
0.0
0.00
0.25
0.50
0.75
1.00
1.25
log Wiping Duration
mixed Predicted Mean
simple Predicted Mean

Figure 17b

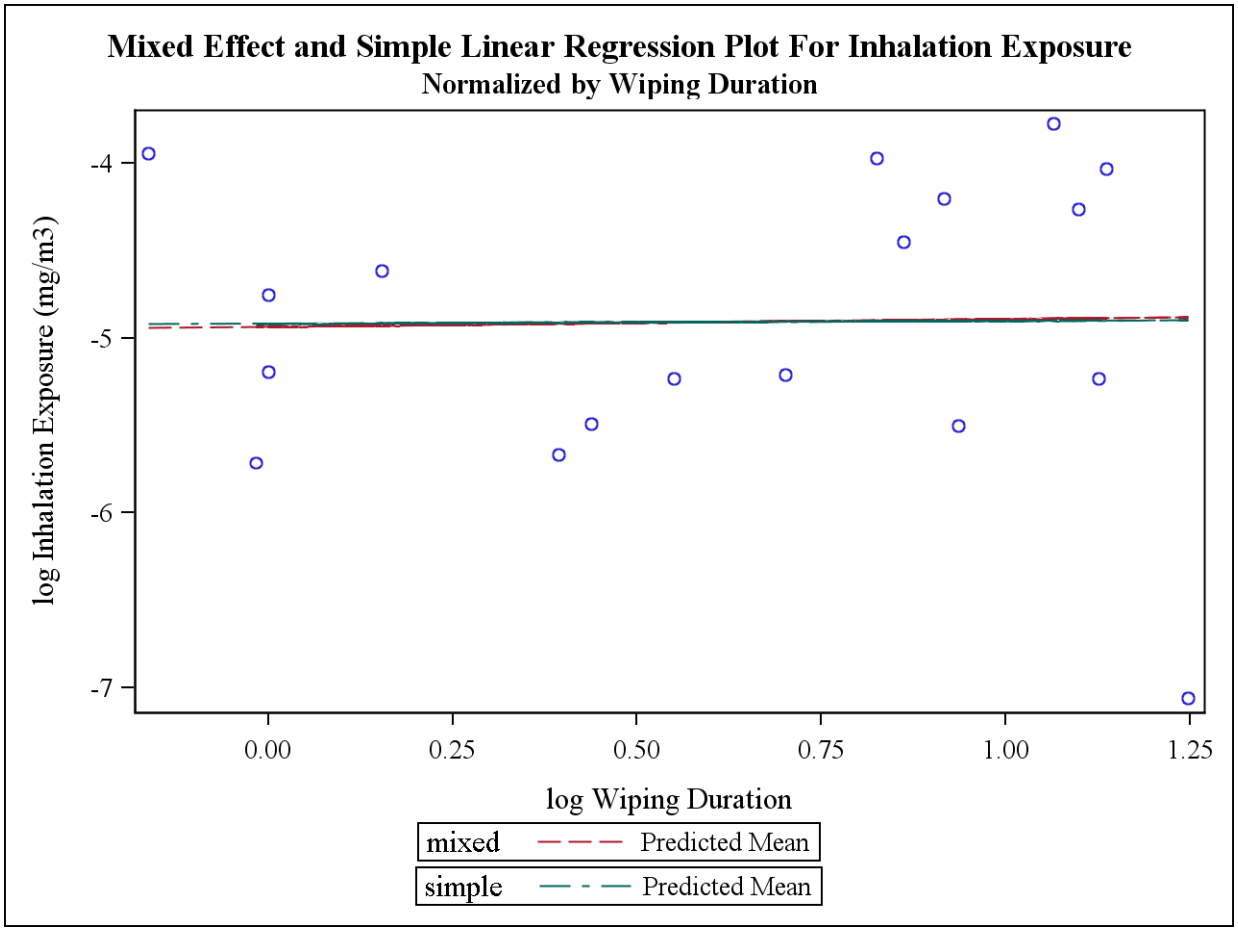
Mixed Effect and Simple Linear Regression Plot For Inhalation Exposure
Normalized by Wiping Duration
log Inhalation Exposure (mg/m3)
-4
-5
-6
-7
0.00
0.25
0.50
0.75
1.00
1.25
log Wiping Duration
mixed
Predicted Mean
simple
Predicted Mean

Figure 18b

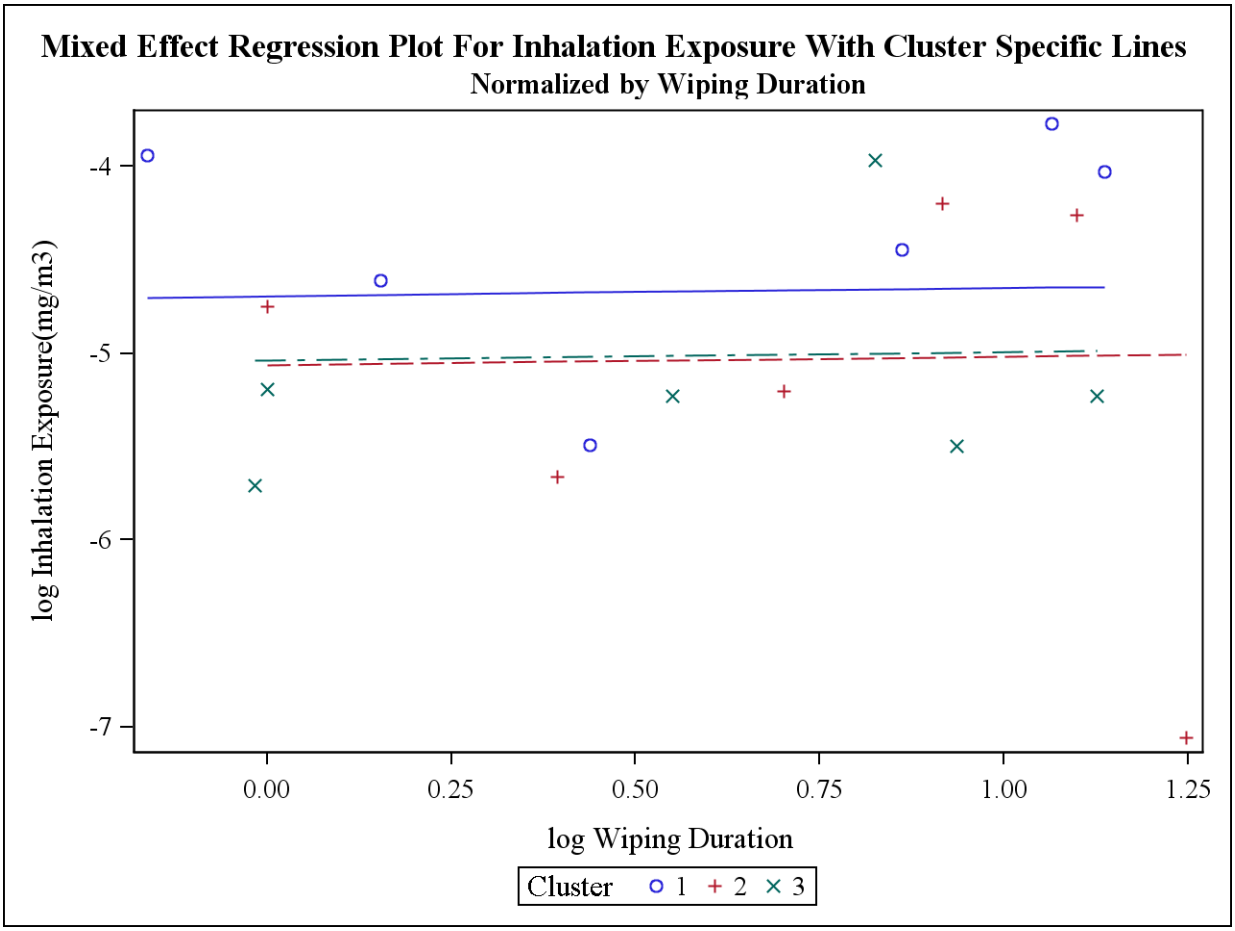
Mixed Effect Regression Plot For Inhalation Exposure With Cluster Specific Lines
Normalized by Wiping Duration
log Inhalation Exposure(mg/m3)
-4
-5
-6
-7
0.00
0.25
0.50
0.75
1.00
1.25
log Wiping Duration
Cluster 1 2 3

Figure 20b

Analyses of inhalation exposure per pounds of active ingredient handled and hours of wiping duration.

Table and Figure Numbers are Consistent with main text (add "c").

Table 1c. Summary statistics for normalized exposure.

Statistic	Normalized Inhalation (mg/m^3/lb AI/hour)
Arithmetic Mean	7.82
Arithmetic Standard Deviation	12.84
Geometric Mean	3.57
Geometric Standard Deviation	3.75
Min	0.12
5%	0.12
10%	0.99
25%	1.90
50%	2.93
75%	7.44
90%	22.71
95%	54.49
Max	54.49

Table 2c. Arithmetic mean and 95th percentile estimates from lognormal mixed model for normalized exposure.

Exposure Route	Clothing	Arithmetic Mean (95% confidence interval)	95th percentile (95% confidence interval)
Inhalation (mg/m^3/lb AI/hour)		8.94 (3.15, 28.92)	33.15 (10.06, 108.51)

Table 6c. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation exposure (mg/m^3/lb AI/hour).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	3.75	2.40	5.98	1.6	2.06	5.89	1.8

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDm	3.88	2.42	6.56	1.7	2.08	6.83	1.9
ICC	0.16	0.00	0.61		0.00	0.61	
GMs	3.57	1.53	8.53	2.4	2.09	5.90	1.7
GMm	3.57	1.53	8.53	2.4	2.09	5.90	1.7
AMs	7.82	2.83	23.02	2.9	3.44	13.43	2.3
AMu	8.56	3.08	25.75	3.0	3.89	18.10	2.2
AMm	8.94	3.15	28.92	3.2	4.00	22.79	2.5
P95s	54.49	9.89	207.51	5.5	8.41	54.49	6.5
P95u	31.43	9.85	97.04	3.2	10.70	69.44	2.9
P95m	33.15	10.06	108.51	3.3	10.96	85.96	3.0

Table 8c. 95 percent confidence intervals for slope of log exposure versus log (pounds of active ingredient × hours of wiping duration).

Exposure Route	**Clothing**	**Model**	**Estimate**	**Lower**	**Upper**	**Confidence Interval Width**
Inhalation (mg/m^3/lb AI/ hour)		Mixed	0.09	-0.33	0.51	0.83
		Simple Linear	0.06	-0.35	0.47	0.82

Table 9c. Quadratic mixed models with 95% confidence intervals for the log exposure log (pounds of active ingredient × hours of wiping duration).

Exposure	**Parameter**	**Estimate**	**Degrees of Freedom**	**Lower Bound**	**Upper Bound**	**GSD**	**ICC**	**Width of Confidence Interval**
Inhalation	Intercept	0.78	14.16	-15.11	16.68	2.44	0.14	31.79
Inhalation	Slope	1.77	14.04	-3.35	6.88	2.44	0.14	10.23
Inhalation	Quad	0.13	13.95	-0.27	0.54	2.44	0.14	0.81

Table 10c. Minimum Pounds of Active Ingredient × Hours of Wiping Duration for Which Normalized Exposure Model Over-Predicts Inhalation Exposure.

Exposure Route	Clothing	Model	Slope	Threshold Level (lb AI hour)
Inhalation (mg/m3)		Mixed	0.09	0.00076

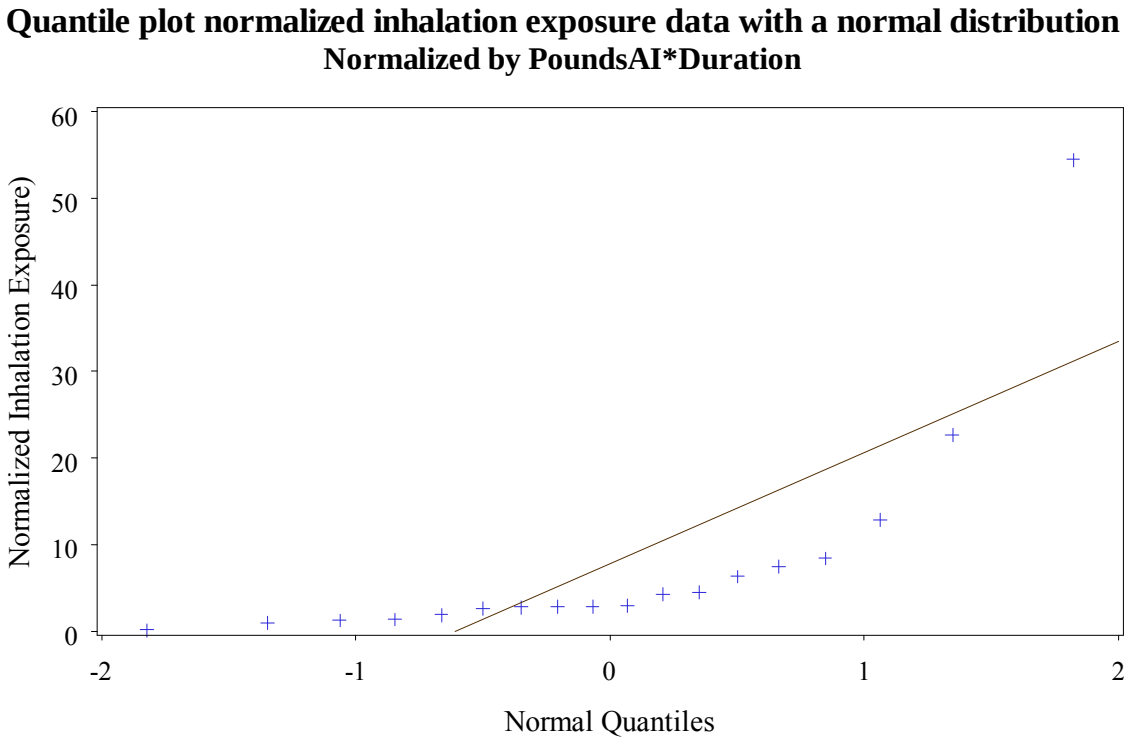

Figure 7c

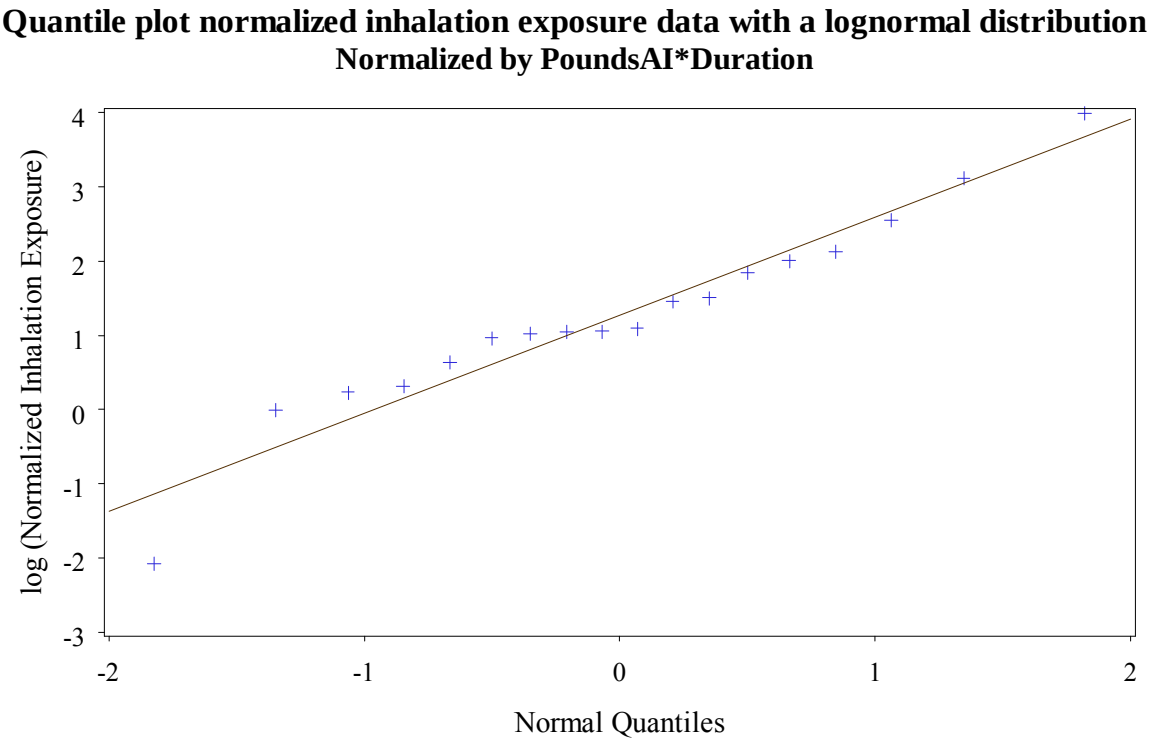
Quantile plot normalized inhalation exposure data with a lognormal distribution
Normalized by PoundsAI*Duration
log (Normalized Inhalation Exposure)
4
3
2
1
0
-1
-2
-3
-2
-1
0
1
2
Normal Quantiles

Figure 8c

Simple Linear Regression of Ln Inhalation Exposure on Ln PoundsAI*Duration
Normalized by PoundsAI*Duration

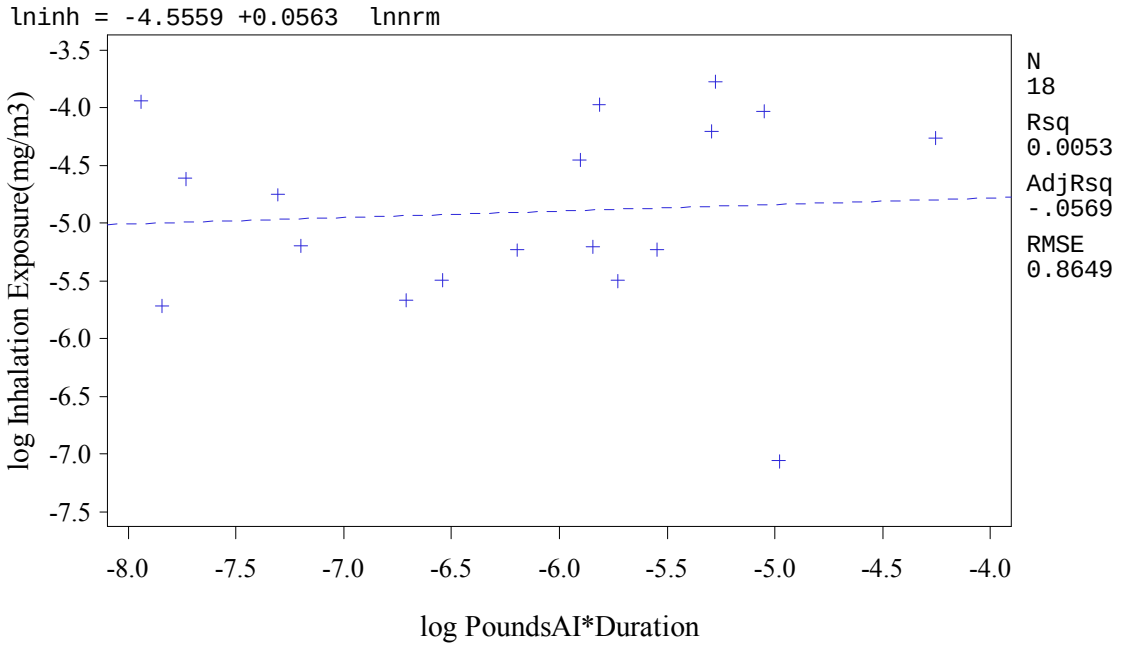

Figure 13c

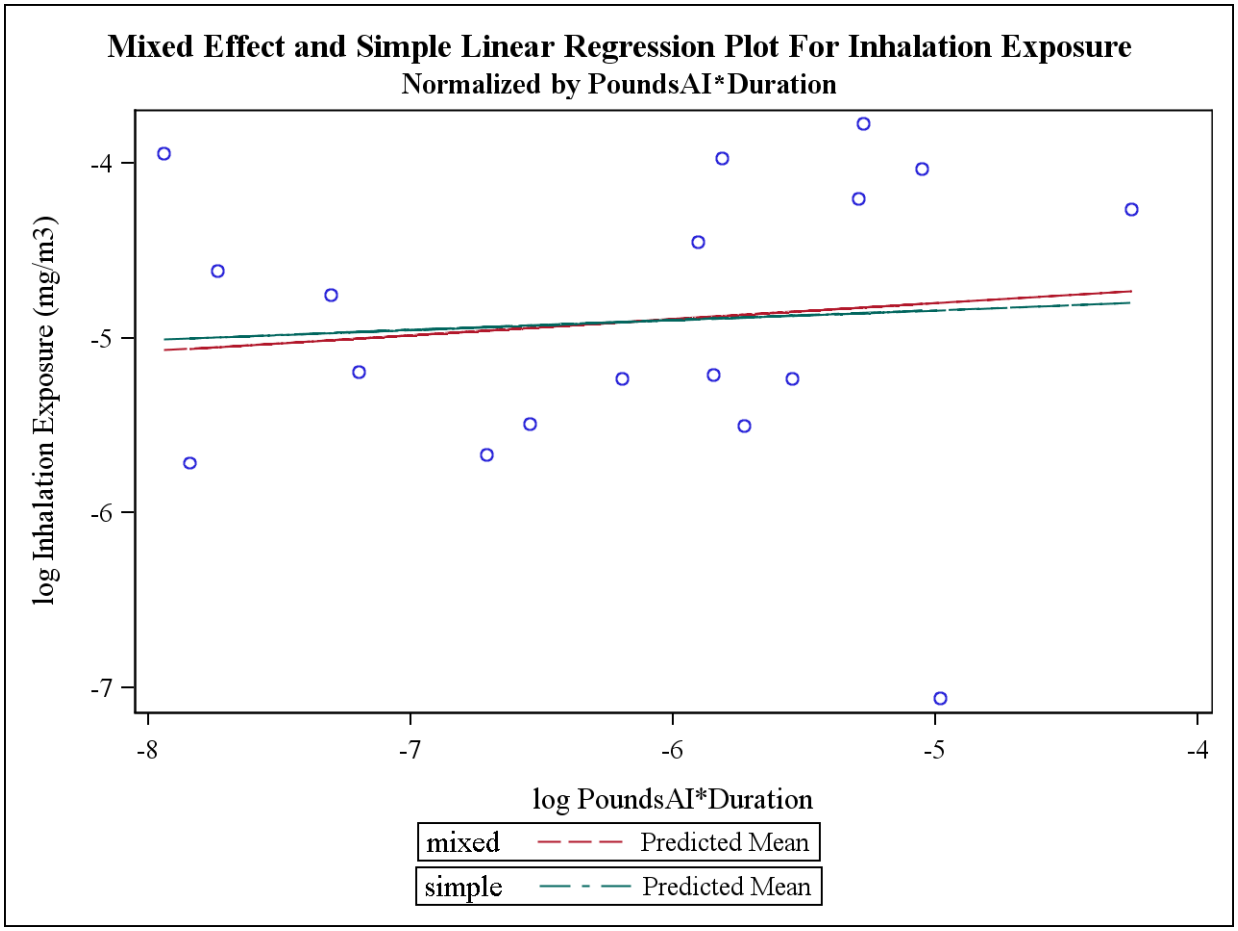
Mixed Effect and Simple Linear Regression Plot For Inhalation Exposure
Normalized by PoundsAI*Duration
log Inhalation Exposure (mg/m3)
-4
-5
-6
-7
-8
-7
-6
-5
-4
log PoundsAI*Duration
mixed
Predicted Mean
simple
Predicted Mean

Figure 18c

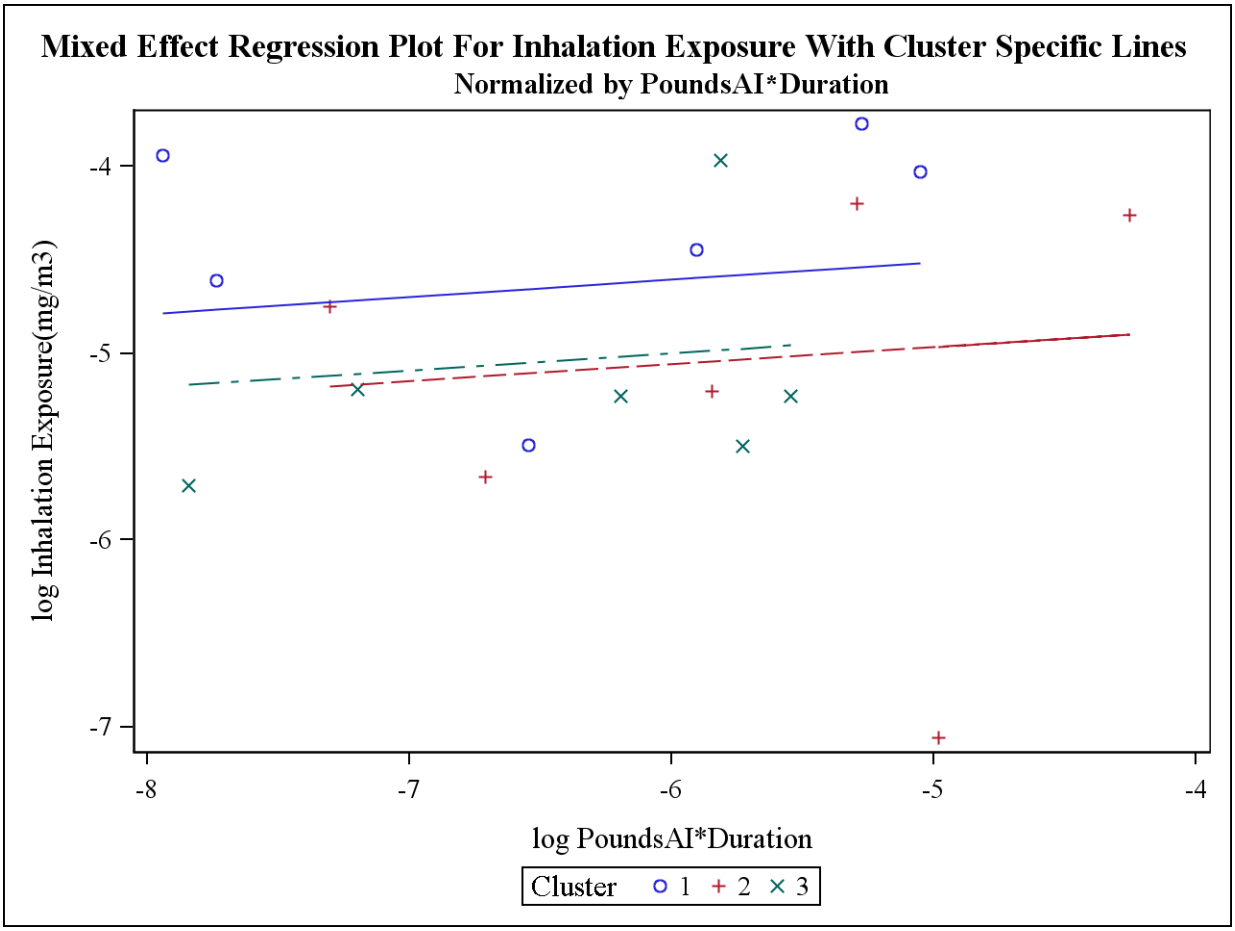
Mixed Effect Regression Plot For Inhalation Exposure With Cluster Specific Lines
Normalized by PoundsAI*Duration
log Inhalation Exposure(mg/m3)
-4
-5
-6
-7
-8
-7
-6
-5
-4
log PoundsAI*Duration
Cluster 1 2 3

Figure 20c

Analyses of inhalation exposure per surface area wiped.

Table and Figure Numbers are Consistent with main text (add "d").

Table 1d. Summary statistics for normalized exposure.

Statistic	Normalized Inhalation (mg/m^3/sq ft)
Arithmetic Mean	0.0000063
Arithmetic Standard Deviation	0.0000044
Geometric Mean	0.0000048
Geometric Standard Deviation	2.5242839
Min	0.0000002
5%	0.0000002
10%	0.0000024
25%	0.0000036
50%	0.0000053
75%	0.0000069
90%	0.0000155
95%	0.0000180
Max	0.0000180

Table 2d. Arithmetic mean and 95th percentile estimates from lognormal mixed model for normalized exposure.

Exposure Route	Clothing	Arithmetic Mean (95% confidence interval)	95th percentile (95% confidence interval)
Inhalation (mg/m^3/sq ft)		0.0000075 (0.0000041, 0.0000142)	0.0000225 (0.0000104, 0.0000481)

Table 6d. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation exposure (mg/m^3/sq ft).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	2.52	1.86	3.44	1.4	1.50	3.91	1.7

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
GSDm	2.56	1.87	3.59	1.4	1.51	4.34	1.7
ICC	0.09	0.00	0.53		0.00	0.54	
GMs	0.0000048	0.0000028	0.0000082	1.7	0.0000032	0.0000067	1.5
GMm	0.0000048	0.0000028	0.0000082	1.7	0.0000032	0.0000067	1.5
AMs	0.0000063	0.0000039	0.0000132	2.1	0.0000046	0.0000082	1.4
AMu	0.0000074	0.0000041	0.0000138	1.9	0.0000051	0.0000104	1.4
AMm	0.0000075	0.0000041	0.0000142	1.9	0.0000052	0.0000117	1.6
P95s	0.0000180	0.0000103	0.0000802	4.5	0.0000085	0.0000180	2.1
P95u	0.0000220	0.0000103	0.0000457	2.1	0.0000100	0.0000372	2.2
P95m	0.0000225	0.0000104	0.0000481	2.2	0.0000101	0.0000434	2.2

Table 8d. 95 percent confidence intervals for slope of log exposure versus log (surface area wiped).

Exposure Route	**Clothing**	**Model**	**Estimate**	**Lower**	**Upper**	**Confidence Interval Width**
Inhalation (mg/m^3/sq ft)		Mixed	0.34	-0.32	1.00	1.32
		Simple Linear	0.35	-0.25	0.95	1.21

Table 9d. Quadratic mixed models with 95% confidence intervals for the log exposure versus log (surface area wiped).

Exposure	**Parameter**	**Estimate**	**Degrees of Freedom**	**Lower Bound**	**Upper Bound**	**GSD**	**ICC**	**Width of Confidence Interval**
Inhalation	Intercept	-15.79	13.89	-61.42	29.85	2.38	0.12	91.27
Inhalation	Slope	2.70	13.79	-10.05	15.44	2.38	0.12	25.49
Inhalation	Quad	-0.16	13.71	-1.05	0.72	2.38	0.12	1.77

Table 10d. Minimum Square Feet Surface Area Wiped for Which Normalized Exposure Model Over-Predicts Inhalation Exposure.

Exposure Route	Clothing	Model	Slope	Threshold Level (sq ft)
Inhalation (mg/m3)		Mixed	0.34	792.1

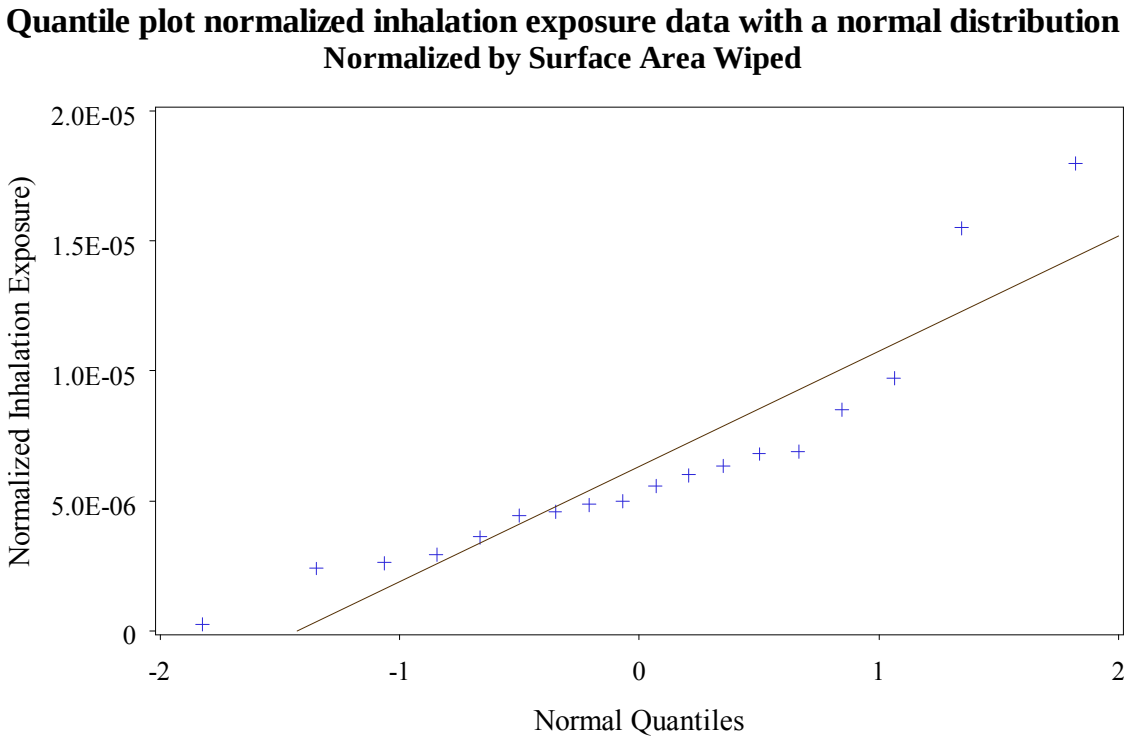

Figure 7d

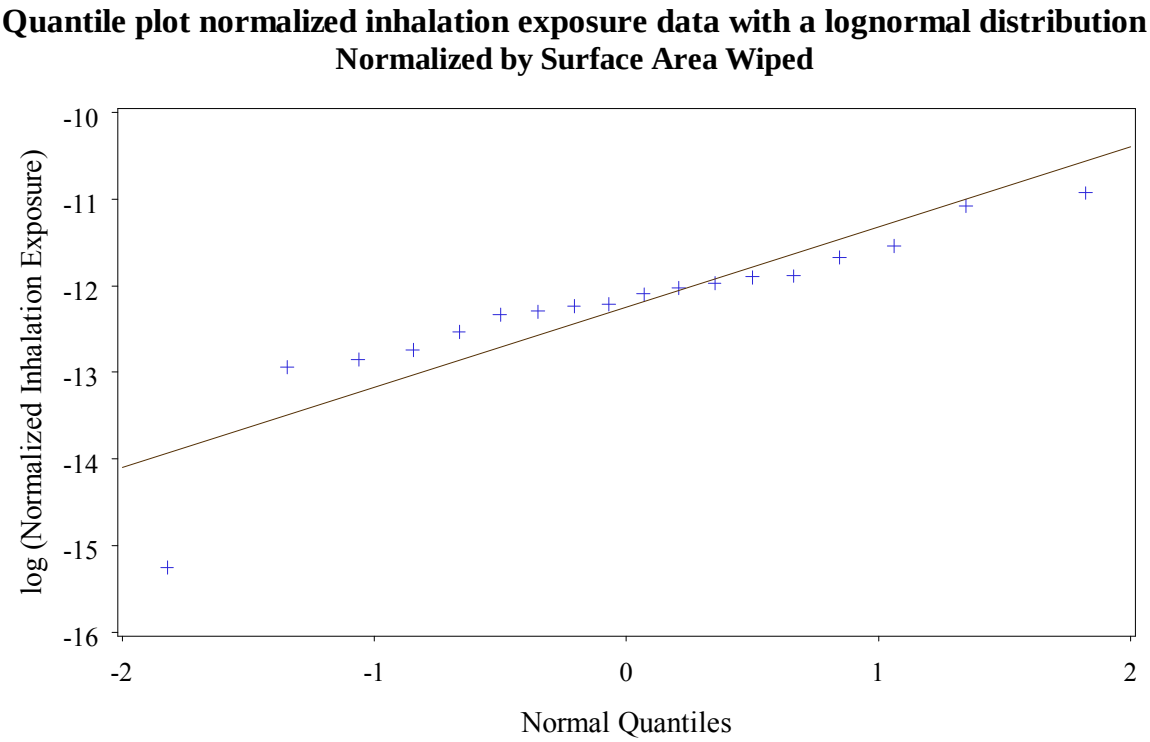
Quantile plot normalized inhalation exposure data with a lognormal distribution
Normalized by Surface Area Wiped
log (Normalized Inhalation Exposure)
-10
-11
-12
-13
-14
-15
-16
-2
-1
0
1
2
Normal Quantiles

Figure 8d

Simple Linear Regression of Ln Inhalation Exposure on Ln Surface Area Wiped Normalized by Surface Area Wiped

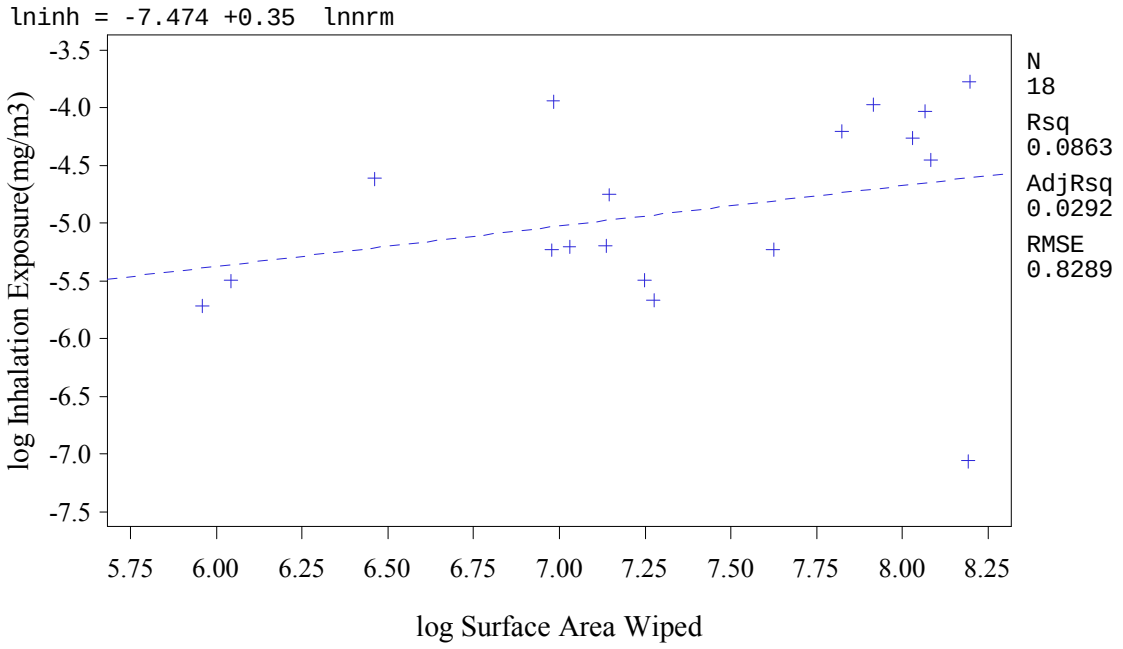

Figure 13d

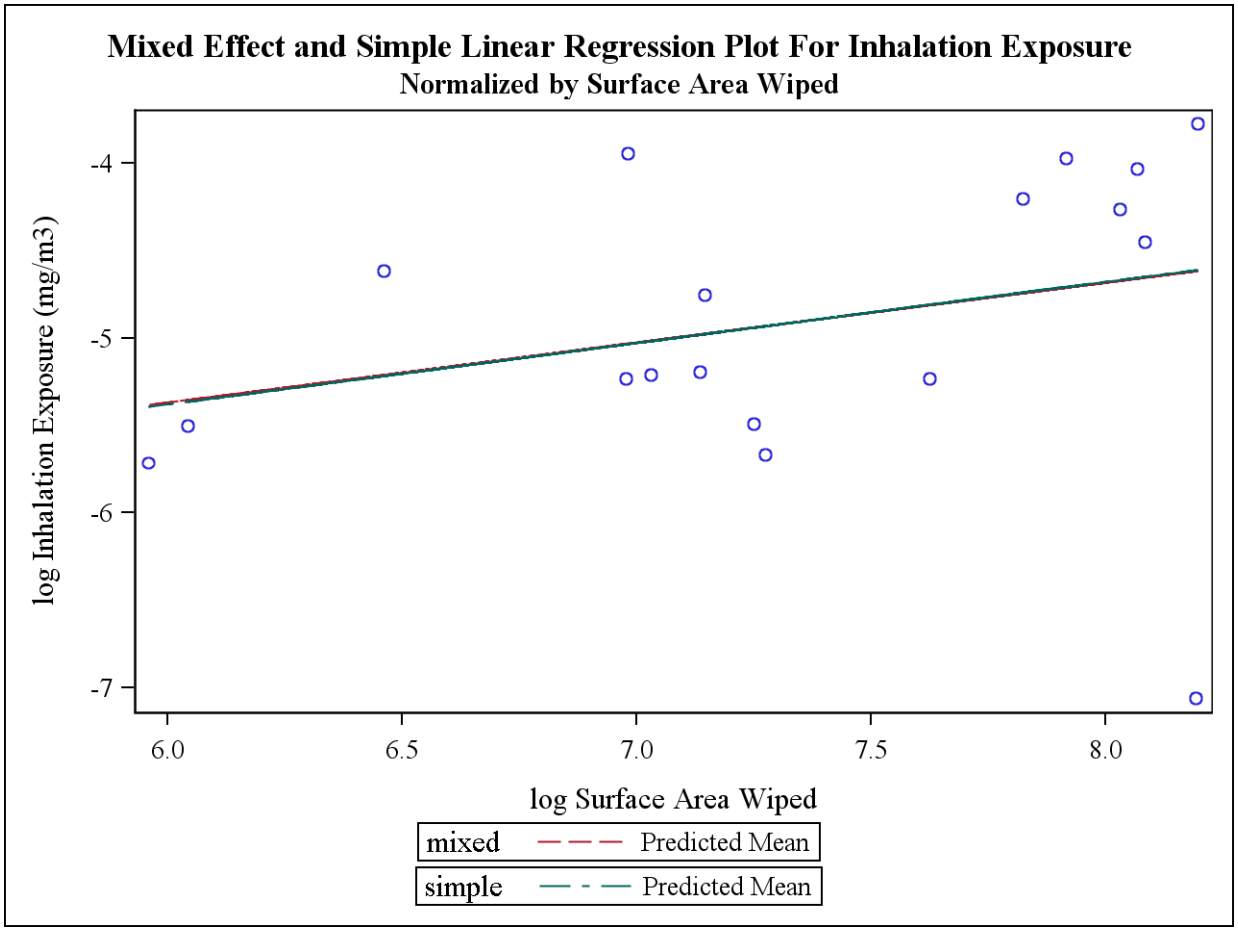
Mixed Effect and Simple Linear Regression Plot For Inhalation Exposure
Normalized by Surface Area Wiped
log Inhalation Exposure (mg/m3)
-4
-5
-6
-7
6.0
6.5
7.0
7.5
8.0
log Surface Area Wiped
mixed
Predicted Mean
simple
Predicted Mean

Figure 18d

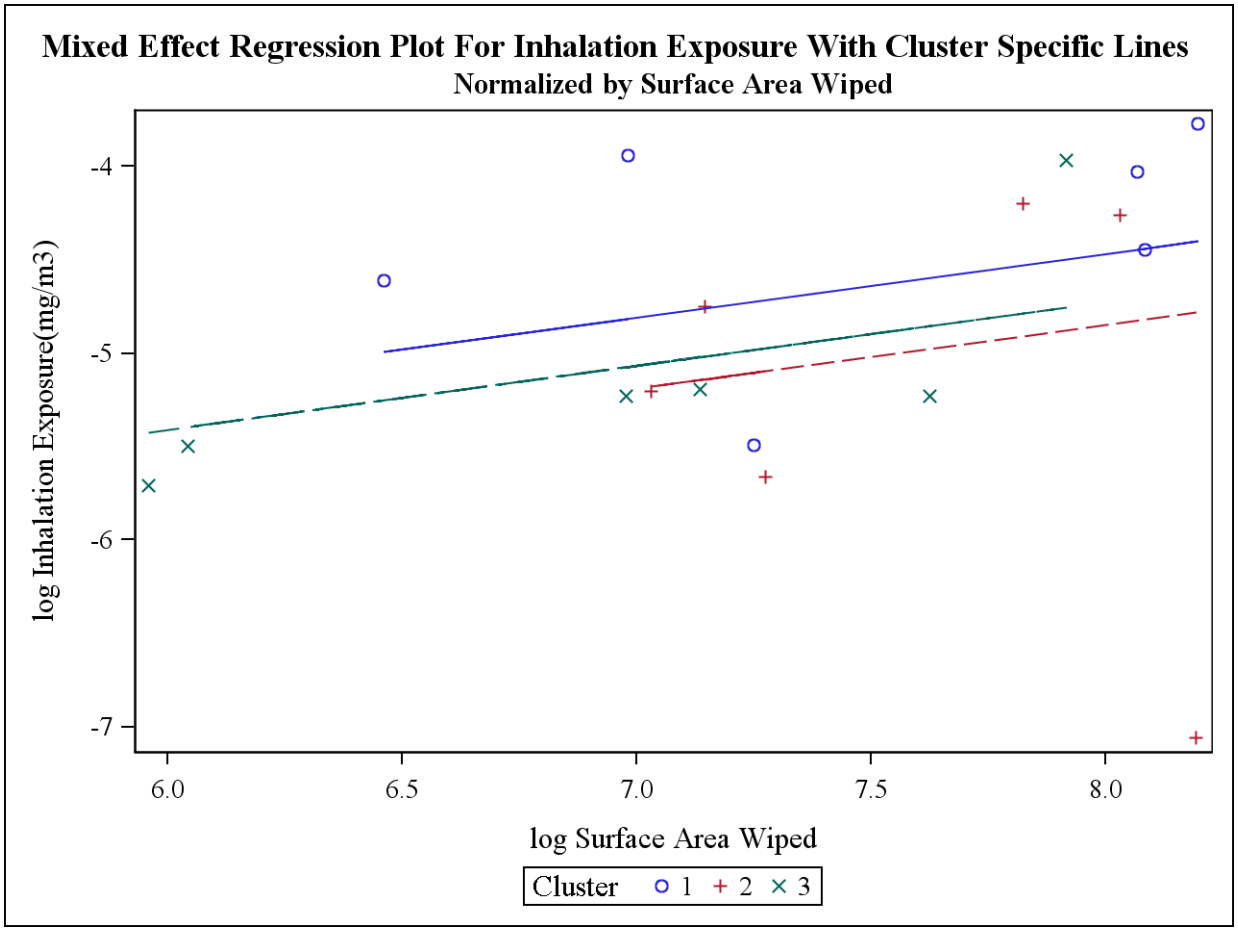

Figure 20d

Analyses of inhalation mass exposure per amount of active ingredient.

Table and Figure Numbers are Consistent with main text (add "e").

Inhalation mass exposure (mg) is estimated as air concentration (mg/m^3) × breathing rate (1 m^3/hour) × wiping duration (hours).

Table 1e. Summary statistics for normalized exposure.

Statistic	Normalized Inhalation (mg/lb AI)
Arithmetic Mean	16.64
Arithmetic Standard Deviation	12.14
Geometric Mean	12.48

Statistic	Normalized Inhalation (mg/lb AI)
Geometric Standard Deviation	2.31
Min	1.52
5%	1.52
10%	6.26
25%	7.71
50%	10.88
75%	27.00
90%	37.82
95%	39.37
Max	39.37

Table 2e. Arithmetic mean and 95th percentile estimates from lognormal mixed model for normalized exposure.

Exposure Route	Clothing	Arithmetic Mean (95% confidence interval)	95th percentile (95% confidence interval)
Inhalation (mg/lb AI)		18.51 (8.53, 42.33)	53.77 (20.47, 143.56)

Table 6e. Arithmetic mean, geometric mean, geometric standard deviation, and 95th percentiles (with 95% confidence intervals and fold relative accuracy), for different statistical models of the normalized inhalation exposure (mg/lb AI).

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	Estimate	Lower Bound	Upper Bound	Fold Relative Accuracy	Lower Bound	Upper Bound	Fold Relative Accuracy
GSDs	2.31	1.70	3.37	1.5	1.78	2.99	1.3
GSDm	2.43	1.70	3.87	1.6	1.83	3.35	1.4
ICC	0.37	0.00	0.77		0.00	0.84	
GMs	12.48	6.25	24.88	2.0	9.21	16.67	1.4
GMm	12.48	6.25	24.88	2.0	9.21	16.67	1.4
AMs	16.64	8.11	36.85	2.2	12.64	20.78	1.3
AMu	17.74	8.34	38.31	2.2	12.97	23.00	1.4
AMm	18.51	8.53	42.33	2.3	13.25	25.09	1.4
P95s	39.37	20.37	174.00	4.4	30.91	39.37	1.3
P95u	49.59	19.90	120.76	2.5	31.05	71.54	1.6

		Parametric Bootstrap			Non-parametric Bootstrap		
Parameter	**Estimate**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**	**Lower Bound**	**Upper Bound**	**Fold Relative Accuracy**
P95m	53.77	20.47	143.56	2.7	32.21	84.53	1.7

Table 8e. 95 percent confidence intervals for slope of log exposure versus log (amount of active ingredient).

Exposure Route	Clothing	Model	Estimate	Lower	Upper	Confidence Interval Width
Inhalation (mg/lb AI)		Mixed	0.94	0.30	1.59	1.28
		Simple Linear	0.77	0.10	1.44	1.34

Table 9e. Quadratic mixed models with 95% confidence intervals for the log exposure versus log (amount of active ingredient).

Exposure	Parameter	Estimate	Degrees of Freedom	Lower Bound	Upper Bound	GSD	ICC	Width of Confidence Interval
Inhalation	Intercept	9.50	13.57	-24.13	43.14	2.50	0.33	67.26
Inhalation	Slope	3.13	13.49	-6.76	13.02	2.50	0.33	19.77
Inhalation	Quad	0.16	13.44	-0.56	0.88	2.50	0.33	1.45

Table 10e. Minimum Pounds of Active Ingredient for Which Normalized Exposure Model Over-Predicts Inhalation Mass Exposure.

Exposure Route	Clothing	Model	Slope	Threshold Level (lb AiaH)
Inhalation (mg)		Mixed	0.94	0.00000086

Quantile plot normalized inhalation mass exposure data with a normal distribution
Normalized by Pounds Active Ingredient Handled

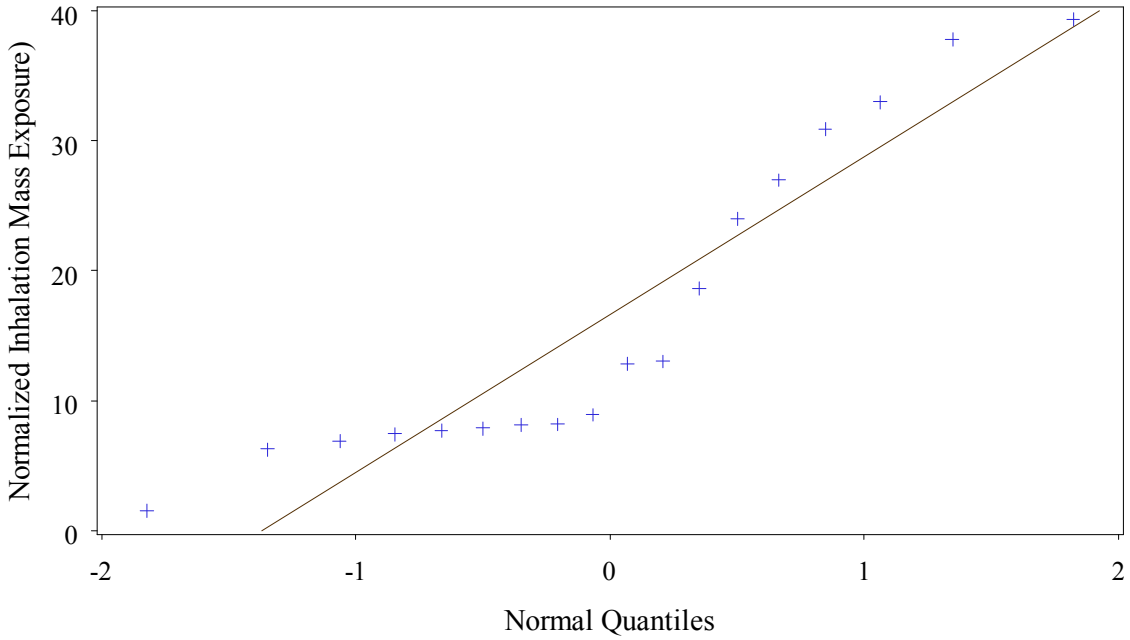

Figure 7e

Quantile plot normalized inhalation mass exposure data with a lognormal distribution
Normalized by Pounds Active Ingredient Handled

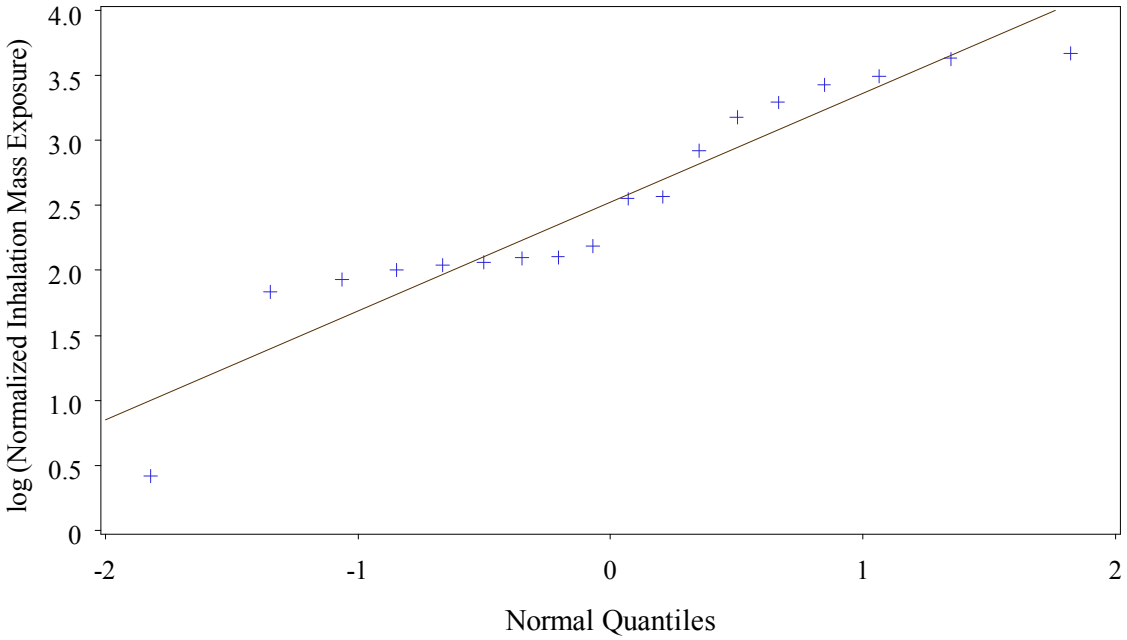

Figure 8e

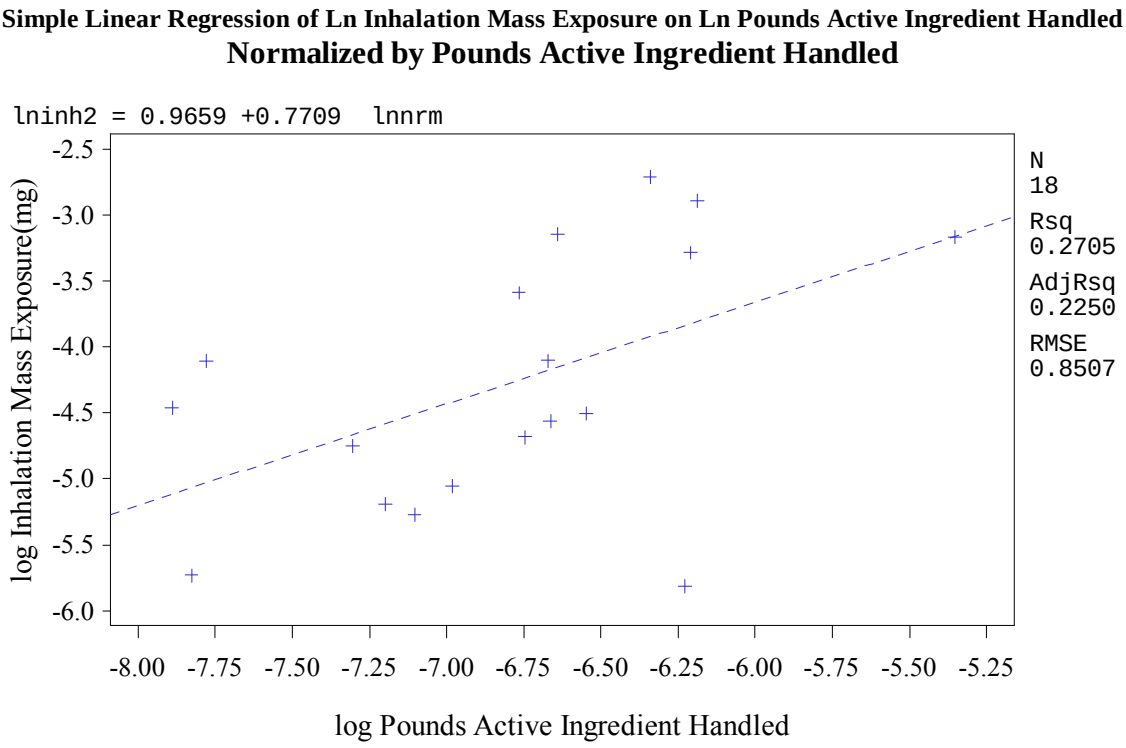
Simple Linear Regression of Ln Inhalation Mass Exposure on Ln Pounds Active Ingredient Handled
Normalized by Pounds Active Ingredient Handled
lninh2 = 0.9659 +0.7709 lnnrm
log Inhalation Mass Exposure(mg)
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
-5.5
-6.0
-8.00
-7.75
-7.50
-7.25
-7.00
-6.75
-6.50
-6.25
-6.00
-5.75
-5.50
-5.25
log Pounds Active Ingredient Handled
N
18
Rsq
0.2705
AdjRsq
0.2250
RMSE
0.8507

Figure 13e

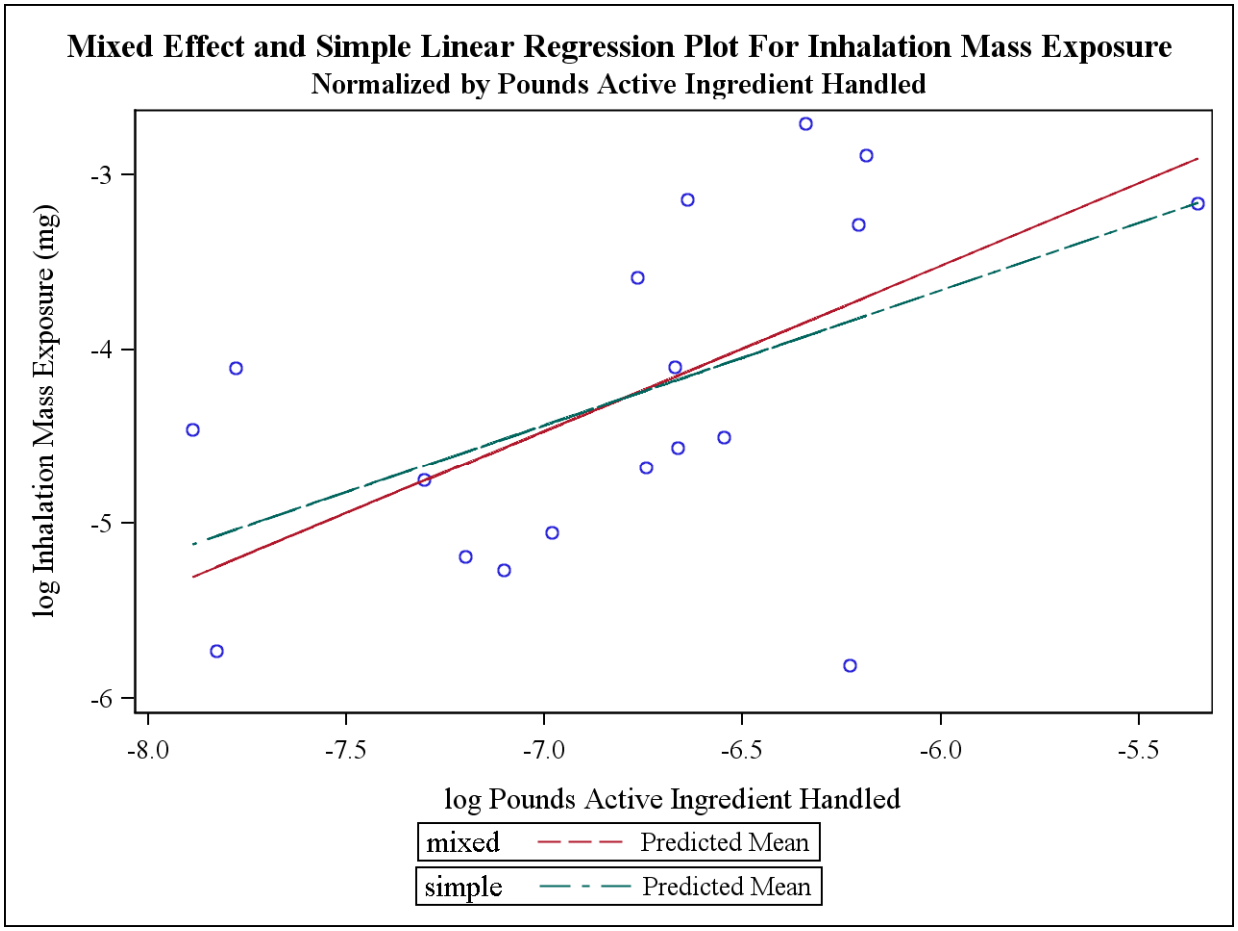
Mixed Effect and Simple Linear Regression Plot For Inhalation Mass Exposure
Normalized by Pounds Active Ingredient Handled
log Inhalation Mass Exposure (mg)
-3
-4
-5
-6
-8.0
-7.5
-7.0
-6.5
-6.0
-5.5
log Pounds Active Ingredient Handled
mixed
Predicted Mean
simple
Predicted Mean

Figure 18e

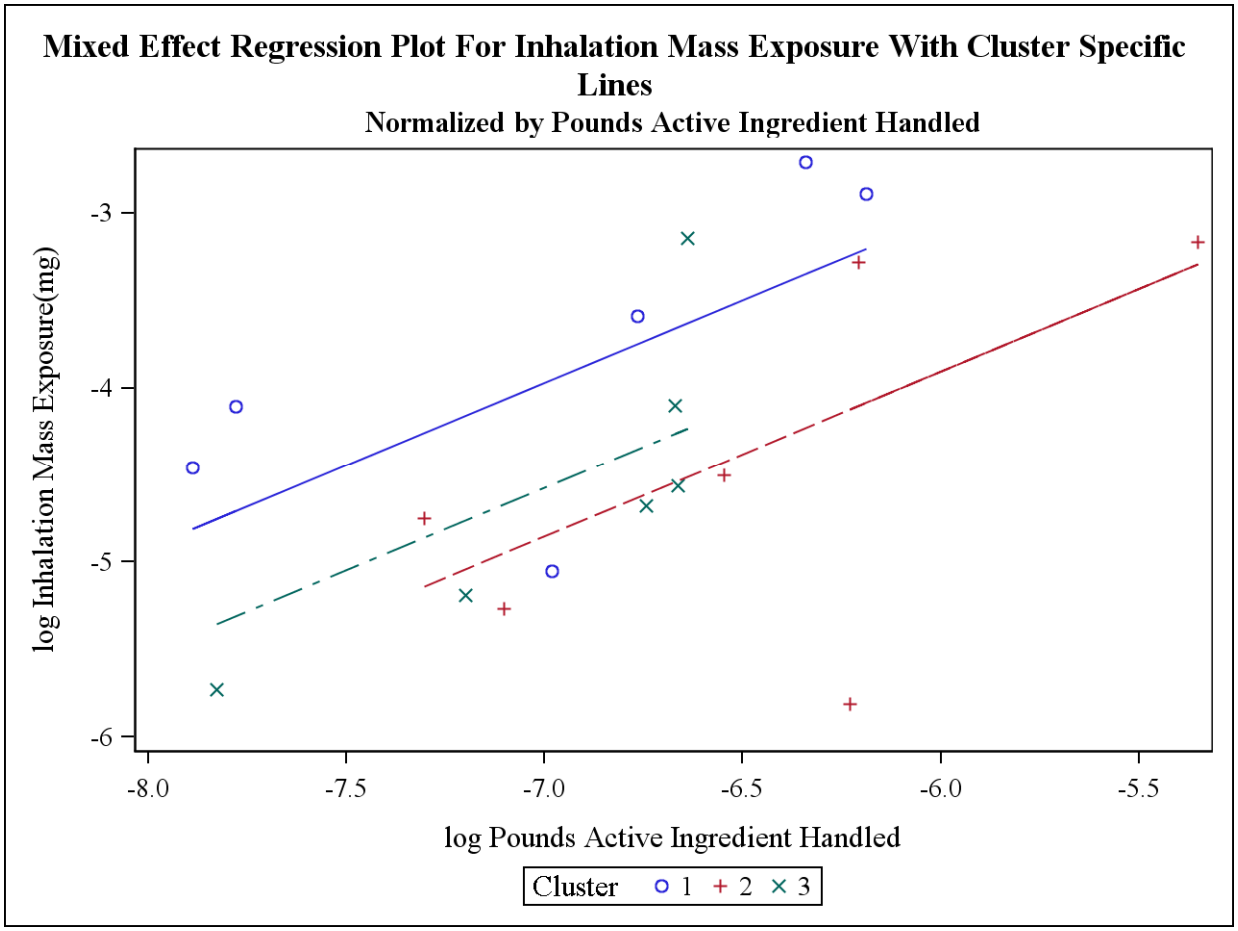
Mixed Effect Regression Plot For Inhalation Mass Exposure With Cluster Specific Lines
Normalized by Pounds Active Ingredient Handled
log Inhalation Mass Exposure(mg)
-3
-4
-5
-6
-8.0
-7.5
-7.0
-6.5
-6.0
-5.5
log Pounds Active Ingredient Handled
Cluster 1 2 3

Figure 20e